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RAYNAUD'S DISEASE

EVIDENCE THAT IT IS A TYPE OF VASOMOTOR NEUROSIS *

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In 1862, Raynaud [1] presented a series of cases under the title of "local asphyxia and symmetrical gangrene of the extremities." He summarized the clinical features as follows:

In the slight cases the ends of the fingers and toes became cold, cyanosed and livid, and at the same time more or less painful. In grave cases the area affected by cyanosis extends upward for several centimeters above the root of the nails; at the same time the nose and ears may become the seat of analogous phenomena. Finally, if this state is prolonged for a certain time we see gangrenous points appear on the extremities; the gangrene is always dry, and may occupy the superficial layers of the skin from the extent of a pinhead up to the end of a finger, rarely more.

VIEWS ON THE MECHANISM OF ARTERIAL SPASM

Raynaud's Hypothesis of Vasomotor Neurosis.—In a second communication in 1874, Raynaud criticized his original title:

First there is always a real inconvenience in giving two distinct names to one and the same object. Local asphyxia and symmetrical gangrene are not two distinct maladies, but two degrees of one and the same malady. Of these two degrees, the second is often absent, which prevents our being able to adopt it as the basis of a precise nomenclature. . . . A really valid objection would arise to the use of the word "local," if it led to the inference that the malady is exclusively local, that is to say, that it is in the affected parts themselves that the origin of the disease is to be sought, which is quite contrary to my view.

Raynaud expressed his conception of the etiology of the disease clearly:

To attribute these phenomena to a fault of vasomotor innervation, was an interpretation which physiology assuredly authorized. I have further main-

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1. Raynaud, Maurice: L'asphyxia locale et de la gangrène symmétrique des extrémités, Paris, 1862.

tained that the marked symmetry of the lesions ought to suggest that they originate in a discharge, either spontaneous or reflex, starting from the cord and radiating thence to the vascular nerves of the extremities. . . .

To sum up in a more definite form, I would say that in the present state of our knowledge, local asphyxia of the extremities ought to be considered as a neurosis, characterized by enormous exaggeration of the excito-motor energy of the gray parts of the spinal cord which control the vasomotor innervation.

There seems to be no doubt that Raynaud regarded the disease, afterward known by his name, as vasomotor neurosis. Although subsequently it was recognized that Raynaud's group of cases was somewhat heterogeneous, the theory concerning vasomotor nerves was not seriously questioned until Lewis brought forward experimental evidence directed against it.

Lewis' Hypotheses of Local Abnormality of the Digital Arteries.—The following views were expressed by Lewis:[2]

The primary cause of spasm of the digital vessels in Raynaud's disease of the common type is not an abnormal vasomotor impulse but a local fault of the vessels.

Our observation upon ulnar nerve anesthesia and our examination of instances of surgical interference with the vasomotor nerves, lead us to the same conclusion at which we arrived from our observation upon local warming and cooling, namely, that a local fault of the vessels, and not a vasomotor impulse, determines the abnormal condition of spasm that the digital vessels exhibit at relatively low temperature.

We have now related our evidence for the belief that the vasomotor system is not deranged in these patients, but that the fault lies in the vessels themselves.

The several writers, we have quoted, in our view have not realized the real significance of the results of sympathectomy because the almost universal acceptation of Raynaud's hypothesis, namely that the spasm of the vessels is primarily due to nervous impulses, has stood in their way. This hypothesis has become strongly entrenched by traditional teaching, but is one which has not been supported at any stage of its supremacy by adequate evidence.

Consideration of the Evidence for Primary Local Fault of the Digital Arteries.—Lewis has performed a great service in indicating experimental methods for investigating Raynaud's disease, the original etiologic conception of which was based almost entirely on clinical observation. We are unable to agree, however, that he has produced convincing evidence that would warrant the discarding of the theory concerning the vasomotor nerves or the substitution of the hypothesis of a local abnormality of the artery.

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2. Lewis, Thomas: Experiments Relating to the Peripheral Mechanism Involved in Spasmodic Arrest of the Circulation in the Fingers, a Variety of Raynaud's Disease, Heart **15**:7 (Aug.) 1929; Observations upon the Reactions of the Vessels of the Human Skin to Cold, Heart **15**:177 (May) 1930.

Lewis' main evidence appears to rest on the production of cyanosis of the fingers after anesthesia of the ulnar nerve or after cervicothoracic sympathectomy. Though in the introduction to his paper the cases are grouped as severe, intermediate and mild, the experimental work on anesthesia and sympathectomy is limited to two severe cases (cases 1 and 2). In both of these cases the condition was of several years' duration, and the complication of dry gangrene of the finger tips was present. It seems unjustifiable to apply conclusions drawn from such advanced cases to the uncomplicated, milder cases, or to use such evidence to formulate an etiologic theory applicable to "Raynaud's disease of the common type." Lewis himself has shown that the digital arteries in severe and in some intermediate cases give a different response to heat than do those in the milder cases. The digital arteries in milder cases apparently responded to heat in the same manner as did the arteries of normal persons. This evidence in itself suggests that some secondary changes take place in the digital arteries in the more advanced stages of the disease. If this is so, and our experiments on cooling also tend to show that such changes do occur, it is obvious that observation of severe, complicated cases should not be used to formulate a conception of an etiologic theory or of a primary mechanism.

Whether anesthetization of the ulnar nerve is an adequate procedure for the interruption of all vasomotor nerves to the little finger is debatable and will be considered more fully later. It is fairly certain, however, that the operation of cervicothoracic sympathectomy does not justify the assumption in any case that all the sympathetic fibers to the hands have been interrupted. The clinical observation of absence of sweating on a warm day or the patient's statement of his own experience does not necessarily decide this point.

Finally, we consider it necessary to examine the behavior of the feet as well as of the hands before formulating a single hypothesis that should be applicable to both.

PRESENT INVESTIGATION

With the exception of some interesting subsidiary experiments, we have confined our main study to the behavior of the extremities after what we have every reason to believe has been complete interruption of the vasomotor nerves. This has been done by local anesthetization or by cervicothoracic sympathectomy. Our object has been to decide between the theory of vasomotor neurosis (Raynaud) and that of local abnormality of the digital arteries (Lewis). So far as theories of etiology are concerned, the investigation is really that of the primary mechanism. We do not attempt to exclude the possibilty of an associated or etiologic dyscrasia of the ductless glands.

In the study of any disease there is danger of confusing the manifestations that occur later with the primary cause. Therefore, we have endeavored to apply our experiments to characteristic cases of the early, uncomplicated type, and from them have deduced our conception of primary mechanism. A study of a second group of more severe and complicated cases has furnished a most instructive contrast.

Local Anesthetization.—Anesthetization of the ulnar nerve does not exclude the possibility of nerve fibers communicating from branches of the median nerve or of short tract fibers from the periarterial plexuses of adjacent arteries such as the palmar arch. Therefore, we have considered it necessary to supplement ulnar anesthetization by regional anesthesia proximal to the base of the fourth and fifth digits. The technic used by Lundy is as follows:

> An anesthetic solution is injected around the ulnar nerve at the elbow, and then field block anesthesia of the small and ring fingers is produced by deep injections made at the bases of these fingers.
>
> A 1 per cent solution of procaine hydrochloride is usually adequate for the period of the experiment. A small amount of epinephrine is added to the anesthetic fluid used for the region of the elbow, but it is omitted from that used for the block anesthesia, which extends more peripherally. In some cases the technic has been modified to elicit special points of investigation.

To obtain a means of being certain that interruption of the vasomotor nerves is complete offers difficulties. One method is to extend the region of anesthesia. We have done this, but the method does not show when the interruption is complete or when it is beginning to decline. Analgesia is a useful indication, but in some of our experiments deep pressure and postural sense returned simultaneously with vasomotor function, whereas diminution of analgesia did not appear until about ten or fifteen minutes later. Full relaxation of the arteries and arterioles, with the surface temperature rising until it reaches approximately 34 or 35 C., is probably the best indication of complete interruption of the vasomotor nerves. A slight rise of temperature may be due to closure of the arteries or to their inability to relax completely under the experimental conditions, but it may also be due to incomplete anesthetization. These considerations are of fundamental importance in interpreting the results of experiments on anesthetization.

Tests for Sweating.—From his experiments on the cat, Langley[3] concluded that the origin and connections of the vasomotor fibers are

3. Langley, J. N.: Further Observations on the Secretory and Vasomotor Fibers of the Foot of the Cat, with Notes on Other Sympathetic Nerve Fibers, J. Physiol. **17**:296, 1894.

identical with those of the secretory (sweat) nerves. The function of the sympathetic nerve fibers is not determined by their nature but by the structures in which they terminate. Therefore, we have used the presence and distribution of reflex sweating as an indication of the presence and distribution of vasomotor fibers. Our subsequent experiments have indicated that Langley's conclusions are applicable to man.

Testing for sweat fibers has been carried out by placing the patient under a full length electric baker fitted with twelve lights. Strips of filter paper, previously dipped in an alcoholic solution of cobalt blue and then completely dried in an oven, are fixed with adhesive strapping over many areas on the trunk and limbs. After thirty minutes, the heater is removed; of course, gross amounts of sweat are easily detected, while the changing of the blue of the filter paper to pink indicates the lesser degrees of perspiration. It is possible to demarcate regions of sweating with considerable accuracy. Positive results are sometimes obtained when the patient's postoperative history and clinical observation suggest that perspiration is completely absent.

Tests With Cold Water.—The whole hand was immersed in water at 15 C. for from fifteen to twenty minutes. The color of the hand was observed throughout the experiment. With long periods of immersion there is a possibilty of "overcooling," even at 15 C.

A bipartite water compartment, of a pattern similar to that employed by Lewis, was used to secure more constant results and more marked cyanosis. The terminal phalanges passed through holes in a rubber partition that separated compartments which contained water of different temperatures. Thus the terminal phalanges were immersed in water at a temperature of approximately 30 C., and the proximal portions of the fingers, with the remainder of the hand, in water at 15 C. The period of immersion was from fifteen to thirty minutes.

The temperature of the laboratory was usually between 23 and 26 C. The majority of experiments, however, were repeated in an ice chamber, of which the atmospheric temperature was from 0 to 4 C.

The degrees of cyanosis were recorded in the order of decreasing severity, as 4, 3, 2, 1. Special color charts were also used for the actual experiments, but their complex numbering is not always clear.

Evidence in Early and Uncomplicated Cases After Local Anesthetization.—In each case, adequate anesthetization of all of the sympathetic nerves that supplied a finger completely abolished and prevented any manifestation of Raynaud's disease in that finger, even under the most extreme conditions.

Changes in color and temperature are the main but not the sole criteria in studying the effects of anesthetization. Redness may replace cyanosis without a sufficient rise in temperature to indicate full relaxation of the arteries and arterioles.

From a study of our cases it will be seen that anesthetization produced complete relaxation of the digital arteries and arterioles, with a

resulting rise of surface temperature to about 34 C.; after anesthetization, psychic stimulation failed to excite cyanosis or to reduce the temperatures of the fingers anesthetized, and the recovery of the surface temperature in the anesthetized finger, after its immersion in cold water, was very rapid and in striking contrast to the signs in the unanesthetized fingers. It is recognized that the tonus of the artery is increased and the amplitude of pulsation diminished by immersion in cold water. This has been shown to occur after section of all of the sympathetic fibers to an affected member in cases of arthritis and in cases of thrombo-angiitis obliterans, as well as in cases of Raynaud's disease. It would be unexpected if cold and hot stimuli failed to have effect on normal smooth muscle. The effect of cold and hot stimuli, however, is a normal phenomenon, and not a distinguishing characteristic of Raynaud's disease.

In this group of uncomplicated cases, the evidence necessitates the conclusion that adequate anesthetization of a finger prevents manifestations of Raynaud's disease in that finger under any circumstances. The primary mechanism of the disorder has been removed by anesthetization.

Evidences in Early and Uncomplicated Cases After Sympathetic Ganglionectomy.—When complete interruption of the sympathetic nerve fibers has been effected, whether of those to the upper limbs (case 5) or of those to the lower limbs (case 6), it has been found impossible, except in case 1, to produce manifestations of Raynaud's disease. In case 1, local mechanical stimulation, with mild local chilling, caused an attack of blanching in the region compressed. The fundamentals were the same as with local anesthetization, except that the nerve fibers were interrupted by operation. The comment in the foregoing section is therefore applicable in all aspects.

By cervicothoracic sympathetic ganglionectomy one sometimes fails to interrupt all of the nerve fibers to the upper limbs (case 6). This can be proved by tests of sweating. In such cases, signs of Raynaud's disease persist and manifest themselves in accordance with the distribution of the remaining nerve fibers. By interrupting the fibers that have survived operation, further local anesthetization can prevent signs of the disease. Therefore, it is concluded that sympathetic ganglionectomy completely prevents the manifestations of typical uncomplicated forms of Raynaud's disease when all nerve fibers have been severed.

The Significance of Psychic Attacks.—Raynaud observed that many of his patients demonstrated general nervous instability. This has also been our experience.

The fact that an attack of blanching or cyanosis of the extremities may follow immediately some slight emotional disturbance (cases 2,

4 and 6) caused by fright, excitement or surprise suggests hypersensitivity of the sympathetic nervous system. Of course, it is possible that the digital arteries are already in a state of abnormal contraction and that the vasomotor effect is just sufficient to complete the spasm, acting merely as an additional and nonessential factor. Against this theory is the fact that such psychic attacks may occur in a warm atmosphere, when the initial temperature of the fingers is fairly high.

It is also possible that a normal person would manifest an equal degree of sympathetic nervous activity under similar circumstances, but that in Raynaud's disease the digital arteries are hypersensitive to such central stimuli. This would constitute an extension of Lewis' hypothesis, of which, however, he does not appear to approve. We, too, are unable to accept this theory in uncomplicated cases, but for different reasons. Apart from the clinical impression that these patients display exaggerated response to emotional stimuli, it is significant that in several of our cases the psychic attack and cyanosis are associated with simultaneous excessive perspiration of the hands. Unless both abnormality of the digital arteries and abnormality of the sweat glands are postulated, it seems necessary to conclude that in cases of Raynaud's disease there is primary hyperexcitability of the sympathetic nervous system.

The Potency of Central Stimuli.—The question arises whether stimuli from the central nervous system overcome a local tendency toward vasodilatation. It has been shown (cases 1 and 2) that if the hand is subjected to a local stimulus such as heat, which is known to produce vasodilatation, the tendency toward the latter may be completely overcome, and actual spasm, with cyanosis, may result from the general effect of cold on the rest of the body.

The Effects of Local Cooling.—It has been found (case 2) that local cooling of one finger may result in cyanosis and fall of temperature in the remaining fingers. This suggests the significance of reflex vasomotor impulses.

In similar experiments Lewis did not obtain such positive results. However, we do not consider our results incompatible with his; it is not suggested that cyanosis will always result. The conditions of the experiment and the relative hypersensitivity of the sympathetic nervous system are obviously important factors.

Lewis pointed out that change of color is not necessarily a criterion of arterial spasm, and this argument might be applied to his interpretation of experiments on local cooling. Leaving aside these considerations, however, we see no reason to deny the possibility that the reflex vasomotor impulses are more intense in the cooled region than in other regions. It is not necessary to ignore the fact that cold may

act on normal smooth musculature, thus rendering the nerve impulses apparently more effective. There seems to be nothing incompatible between Lewis' results of overcooling and a theory based on the functions of vasomotor nerves. Our results might be thought to support the latter theory. Direct methods of testing (anesthetization, sympathectomy), however, tend to produce more decisive evidence.

The Significance of Blanching Fingers.—Lewis stated:

> The theoretical importance of a blanched skin (color K) lies in the fact that simple arterial obstruction will not produce it, provided that, as is usual, the hands lie below the level of the heart, and in the fact that a strong vasoconstrictor nervous impulse can probably produce full blanching of the skin by causing contraction of the minute vessels. If it could be shown in our patients that blanching of the fingers may be due to active contraction of the minute vessels, then such contraction would, in the absence of other equally reasonable explanation, constitute evidence favoring the hypothesis of vasomotor impulses.

We are in complete agreement with this view. Lewis stated, however, that he had never seen an attack commencing with blanching, and he attributed the discrepancy between his experience and his patients' statements to the fact that when patients note the abnormality, the hands are not at rest. Our experience with relatively early cases is compatible with our patients' statements that attacks may begin with blanching. We have seen blanching of the fingers occur with the hands at rest and below the level of the heart, and one such case (case 2) is described in detail. The attack was produced by a psychic stimulus, and we consider that the vasomotor nervous mechanism, as suggested in Lewis' hypothetic statement, is the most likely explanation in this case. This does not imply that blanching may never occur by a different mechanism, following sustained arterial spasm. However, sudden blanching as an initial manifestation of an emotional upset is much more probably a vasomotor nervous phenomenon.

It frequently happens that, at the beginning of the disease, only severe blanching occurs; later, blanching followed by cyanosis, and still later, cyanosis only. This may be due to some change in the tonus of the minute vessels and may explain the rarity of the occurrence of blanching with the hands at rest in the more severe cases. The decrease of tonus in the capillaries and smallest venules may have a chemical basis, the effect of stasis.[4]

Evidence in Severe and Complicated Cases.—The results obtained in severe and complicated cases are in sharp contrast to those in milder

4. Brown, G. E.: Observations on the Surface Capillaries in Man Following Cervicothoracic Sympathetic Ganglionectomy, J. Clin. Investigation **9**:115 (Aug.) 1930. Crawford, J. H.: The Influence of the Sympathetic Nervous System on the Capillaries During Passive Congestion, J. Clin. Investigation **7**:527 (Oct.) 1929.

cases. We have found that if all sympathetic fibers are interrupted by local anesthetization, or by operation, it is possible, nevertheless, for the arteries of certain digits to enter into spasm, with resulting cyanosis. This is in keeping with Lewis' observations in severe cases. In these cases, the response to cold is favorably modified by section of the sympathetic nerves, but it is not abolished. It is therefore reasonable to conclude that in severe, complicated cases there is an abnormal response of the arteries, most striking in the fingers that have undergone ulceration of the tip. This is attributed to secondary changes that had taken place in the arteries and arterioles. As regards both changes in color and rate of recovery of temperature after cooling, the difference of behavior of an ulcerated finger and that of an adjacent, intact finger (case 8) is significant. Apart from actual thrombosis, it is conceivable that less grossly morbid changes or severe functional effects in the arterial walls could profoundly modify their response to cold. Such effects might be produced by recurrent severe and prolonged attacks of cyanosis, without gross chronic ulceration necessarily supervening.

Psychic stimuli were effective only before operation and were impotent after the interruption of all nerve fibers.

Although an abnormal response of the artery to cold has been demonstrated, the psychic attacks of cyanosis in the presence of nerve fibers also suggest abnormal hyperactivity of the sympathetic nervous system. An alternative, and possibly supplementary explanation, is an abnormal response of the arteries to psychic stimuli as well as to cold. In favor of an abnormality of the nervous system is the observation of simultaneous sweating that occurs with psychic attacks. It would thus appear that in severe and complicated cases of Raynaud's disease there is a dual abnormality of the sympathetic nervous system and of the digital arteries, the latter in our opinion being a secondary complication.

COMMENT

We believe that it has been shown conclusively that in early and relatively mild, uncomplicated, typical cases of Raynaud's disease, the abnormality lies in the sympathetic nervous system. With complete interruption of nerve fibers by anesthetization or operation, there are no longer signs of Raynaud's disease in the denervated extremity. In this group of cases there was no evidence of abnormality of the digital arteries.

In severe and complicated cases there is abnormality both of the sympathetic nervous system and of the digital arteries. In view of the evidence found in cases in which there is ulceration of certain

fingers and the contrasting behavior in early cases, it seems probable that the abnormality of the arteries is a late effect of the disease.

In our experience, lumbar sympathetic ganglionectomy has never failed to abolish all manifestations of the disease in the feet. This is due to the certainty with which the anatomic structure can be attacked and to the fact that the feet are much better protected from secondary complications. The possibility of arteries of the feet undergoing changes similar to those observed in the hands in severe cases is not denied.

Whatever view is taken of the cause of the abnormality of the digital artery in complicated cases of Raynaud's disease, we cannot conceive on what grounds it could be cited as an etiologic agent or as the essential primary mechanism. Any theory of the primary mechanism of Raynaud's disease must be applicable both to early and to late cases of the disease and to both hands and feet. In our opinion, the sum total of the evidence furnishes an experimental confirmation of Raynaud's original view that there is a primary abnormality of the sympathetic nervous system.

SUMMARY

Raynaud's view of vasomotor neurosis is cited.

Lewis' evidence that the abnormality is in the digital arteries and not in the sympathetic nervous system is considered. The main criticism of his evidence is the limitation of his essential experiments to severe or complicated types of disease.

In the characteristic but uncomplicated cases of the disease, complete interruption of the sympathetic nerve fibers by local anesthetization or by surgical operation prevents any manifestation of the disease.

Cervicothoracic sympathetic ganglionectomy occasionally fails to give complete relief because of failure to section all the sympathetic fibers. In our experience, lumbar sympathetic ganglionectomy is always completely successful.

Three of the nine cases reported in this paper were severe. In all of these severe cases, whether or not ulceration of the fingers was present, interruption of all nerve fibers by anesthetization or by operation alleviated but did not prevent spasm of the digital arteries. In these cases there was an abnormal response of the arteries. The evidence indicates that this is probably a secondary complication. Six of the cases were early and mild. In five of them, interruption of all nerve fibers by anesthetization or by operation alleviated and prevented spasm of the digital arteries. In the one exceptional case of the six, a case of nine months' duration, arterial spasm could be elicited by local application of cold combined with pressure. The case was atypical in other respects also. Apparently, in this case local hyperirritability of the small vessels persisted to some degree after operation.

Any theory of Raynaud's disease must be applicable to early and late cases and to the hands and feet. The great preponderance of our experimental evidence confirms Raynaud's original view of an abnormality of the sympathetic nervous system. On the other hand, in case 1, the factor of primary, persistent, local vascular fault is not excluded.

REPORT OF CASES [5]

CASE 1.—A woman, aged 35, gave evidence of the presence of recent, uncomplicated Raynaud's disease. The history was unimportant, except for periodic frontal headaches associated with nausea and vomiting and induced by emotion, which suggested migraine.

The changes in the color of the skin had commenced nine months prior to examination, and had affected the hands, feet and nose. At first, only blanching occurred, but later there was also a cyanotic phase. The attacks were produced by the slightest change of temperature, such as that experienced on getting out of bed or in going from one room to another, and they occurred in summer as well as in winter. Temperature, emotion or psychic stimuli were also efficacious in producing changes in the color of the extremities. These psychic attacks were usually associated with simultaneous sweating of the hands. Emotion might produce sweating without changes in color, and the hands would become cold and clammy. Micturition was a frequent cause of changes in the color of the hands. The patient believed that this occurred even in the absence of any change of temperature. Apart from changes of color, the hands and feet sometimes became swollen and painful in the cold.

Special Examinations Before Operation.—The right little finger was placed in a jar of water at 15 C. for thirty minutes; the remaining fingers were exposed to the temperature of the room, 26.3 C. Within ten minutes there was a trace of cyanosis in all the fingers, and after twenty minutes this became marked. Cyanosis of the immersed finger gave way to redness after twenty minutes, possibly owing to overcooling. The temperatures of the index fingers of both hands after their removal from the water were taken at intervals of five minutes throughout the experiment, and a progressive fall in degrees centigrade was noted as follows: right index finger, 28.4, 26.7, 25.8, 25.5, 25.3, 25.2, 25.2; left index finger, 28.0, 27.1, 27.0, 26.8, 26.1, 25.7, 25.6. The initial temperature of the little finger was 27.9 C., and the final temperature was 22.5 C.

The patient's hands were warmed in a large blanket and then were exposed to room temperature (24.8 C.) until their temperature was approximately constant. The readings were as follows: [6] R_2, 31.4; R_3, 31.3; R_4, 31.2; R_5, 31.7; L_2, 30.9; L_3, 31.0; L_4, 31.2; L_5, 30.9. The patient was placed with her back to the door, which was then opened, permitting a slight draught to blow from the passage. The temperature of the passage was 23.6 C. Almost immediately the fingers turned blue (graded 2) and their temperature fell, as is indicated in the following readings: R_2, 23.7; R_3, 23.7; R_4, 23.6; R_5, 23.2; L_2, 24.6; L_3, 24.6; L_4, 24.5; L_5, 24.2.

5. The peripheral arteries showed normal degrees of pulsations in all cases.

6. The capital letters "R" and "L" indicate "right" and "left"; the numerical subscripts, the finger concerned. Thus, the expression "R_2" means "right second finger."

The fingers were warm and of good color. The room temperature was 24.2 C. The left hand, including the wrist, was immersed in water at 15 C. for twenty-five minutes. All of the fingers became deeply cyanosed in ten minutes; the hand also had a bluish tinge. In twenty minutes the fourth finger began to turn bright red, which was followed by redness of the third finger; this was probably due to overcooling. The hands were removed from the water and studies of temperature were made; the results are recorded in table 1. Pulsations at the wrist and palm were recorded by a Tycos oscillometer before and after immersion. The pulsations of the wrist were appreciably reduced, and those of the palm were almost obliterated.

The patient's right hand and forearm were covered with a double layer of woolen blanket wrapped several times around the limb so that no draught could possibly penetrate to it. After five minutes, the hand was examined and was found to be hot and sweating; the average temperature of the fingers was 33.4 C. The blanket was then carefully replaced, and the patient was taken for a five minute walk; the temperature outside was 18 C. On reentering the examining room, the hand, when uncovered, was found to be bluish, with irregular mottling.

TABLE 1.—*Temperature of Fingers in Degrees Centigrade Before Operation, Showing Effects of Immersion in Cold Water* *

Time, a.m.	L_2	L_3	L_4	L_5
9:30	29.3	29.2	29.9	29.6
9:35 Immersion in water at 15 C. for 25 minutes				
10:00	21.3	21.6	20.8	21.6
10:10	27.0	26.3	26.0	27.8
10:15	27.0	28.5	28.5	28.9
10:30	30.0	30.5	30.5	30.3

* The temperature of the room was 24.2 C.

The hand was again warmed and was placed in the woolen blanket. After ten minutes the patient was taken into the ice chamber, where the temperature was 2 C. After five minutes, the patient, who was thinly clad, began to shiver. On reentering the examining room (temperature, 25.4 C.) and removing the blanket, the whole hand was seen to be cyanotic, the fingers markedly so. The average temperature of the fingers was 25 C. The palm, however, was covered with perspiration; its temperature was 30.1 C. Within a few minutes patches of red appeared all over the hand and fingers, and five minutes later the whole hand was red.

During the course of these investigations, cyanotic discoloration of the fingers was seen to occur frequently at room temperatures of from 24 to 27 C., with the slightest provocation. A physician entering the room, the cry of another patient, the banging of a door, the falling of an electric fan and the anticipation of an experiment were adequate stimuli for the immediate production of cyanosis of the fingers and a fall of surface temperature. These psychic attacks of cyanosis were associated with simultaneous grossly perceptible perspiration of the hands, which became cold and clammy.

The usual ulnar anesthesia combined with regional anesthesia was undertaken, but to avoid pain to this nervous patient the latter was limited to the fifth finger. Informing the patient of the intended procedure was sufficient to produce an attack of cyanosis when the temperature of the room was 24.6 C. Anesthetization not only abolished the cyanosis in the fifth finger, but caused a rise of temperature of 10 C. (fig. 1). The final temperature of 33.4 C. suggested

that complete relaxation of vessels that previously had been in spasm had taken place. The hand (left) subsequently was placed in water at 15 C. for twenty minutes. At the end of that time it was removed from the water and all the unanesthetized fingers were deeply cyanotic (graded 4), but the fifth finger remained red, without a trace of cyanosis or blanching. The anesthetized portion of the fourth finger was red. The temperature of the fifth finger (table 2) was almost as low as that of the others immediately after removal from the water, but its temperature rose at a much faster rate and reached 34.4 C. in thirty minutes. The average temperature of the remaining fingers was then only approximately 25 C.

The patient was then taken to an ice chamber (temperature, 2 C.) and the immersion in water was repeated with similar results. Traces of cyanosis or

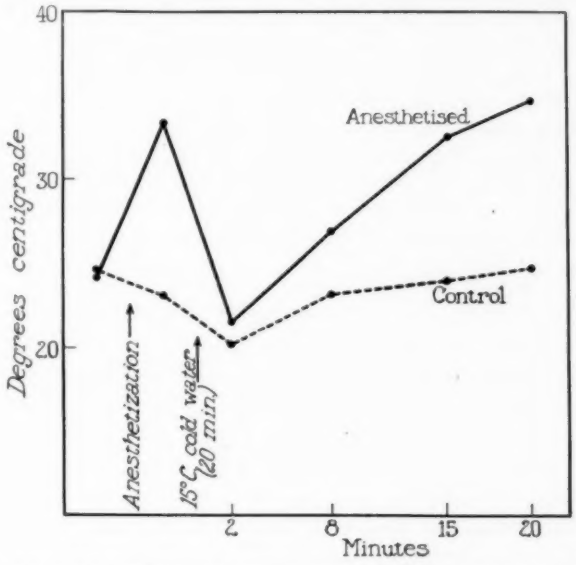

Fig. 1 (case 1).—Effects of ulnar anesthetization and of regional anesthetization applied to the little finger on the surface temperature of the little finger.

TABLE 2.—*Temperature of Fingers in Degrees Centigrade Before Operation, Showing Effects of Anesthetization* *

Time, a.m.	L_1	L_2	L_3	L_4	L_5
10:00	24.4	24.6	24.6	24.2	24.2
Anesthetization of ulnar nerve and L_5					
10:20	23.0	23.1	23.0	23.1	23.4
Immersion in water at 15 C. for 20 minutes					
10:42	19.8	20.1	20.0	20.2	21.5
10:48	22.4	23.2	23.2	24.0	27.0
10:55	23.3	24.0	24.0	26.5	32.6
11:00	24.0	24.7	25.0	27.6	34.4
11:10 to 11:30 Patient in ice chamber at 2 C. with hand in water at 15 C.					
11:40	21.8	21.5	22.0	24.0	29.0
11:55	26.0	27.6	27.7	28.6	33.6

* The temperature of the room was 24.6 C.

blanching were not present in the anesthetized fifth finger at any time. Bilateral cervicothoracic sympathetic ganglionectomy was performed.

Special Examinations After Operation.—The hands were warm and dry two months after operation, and pain or discomfort had not been felt since the operation. The patient stated that she had noticed attacks of pallor when she handled cold or cool objects, if a certain amount of pressure was exerted. This local mechanical stimulus had been necessary for the production of spasm. Changes in color had not been noted in the hands as the result of any of the factors that produced them before operation, such as micturition or emotional upsets.

The patient was placed under an electric heater until profuse sweating was induced over the body and lower parts of the limbs. There was complete absence of sweating of the hands, arms, face and upper part of the thorax. This experiment showed that the sympathetic nerves to the hands had been completely interrupted.

With the room temperature at 24 C., the temperatures of the various fingers were as follows: L_1, 31.0; L_2, 30.1; L_3, 29.6; L_4, 29.3; L_5, 29.6; R_1, 31.4; R_2, 30.6; R_3, 30.7; R_4, 30.8; R_5, 30.5.

The hands were exposed to cold; there were no changes in color until the tips of the fingers were massaged. A definite attack of pallor was then produced. The distal portions of the second and fifth fingers on each hand gave this reaction. The changes in the other fingers were equivocal. Definite cyanosis was not seen. The color became normal in a warm atmosphere.

Comment.—The fact that pallor of the digits could be induced after operation suggests that this case represents one with a local fault of the digital vessels as described by Lewis. It was fairly clear that the operation was complete, yet spasm of the small vessels of the skin could still be induced by local stimulation. In many respects this patient's case was atypical. Before operation, the induction of changes in color by slight stimuli, the lessened effect of cold in the production of changes in color and the marked degree of pain and swelling suggest that factors other than vasomotor disturbance were present. We believe that this case represents an example of irritability of the blood vessels persisting after complete block of the sympathetic nerves to the hands. The clinical result of the operation was excellent. Another point suggesting that this patient's case was atypical was that after operation spasm could be produced in the fingers by pressure when the hands were subjected to slight grades of cooling temperatures of from 26 to 28 C.

Case 2.—A woman, aged 44, had had cold hands for many years, but following the birth of an only child, six years prior to examination, she had noticed changes in color. At first there was only blanching, and later, blanching and cyanosis, and sometimes only cyanosis. Originally the attacks occurred in the winter, but later the chilly portion of a summer day was sufficient to produce changes in color. In the last year, emotional stimuli, even on a warm day, would cause changes in color. All the fingers were involved; the patient believed that the fourth finger of the right hand was the one first affected. For two years there had been attacks of coldness and numbness of the feet, without definite changes in color. It was evident that we were dealing with an uncomplicated case of Raynaud's disease of several years' duration.

Special Examinations.—With a room temperature at 26 C., the right hand was placed in water at 15 C. The left hand was placed in a bipartite water chamber; the terminal phalanges were at a temperature of 30 C., and the remainder of the hand, at 15 C. While the fingers of the right hand were in the water, they underwent a temporary phase of blanching. After thirty minutes, the hands were withdrawn and all the fingers of both hands were cyanosed; the extent of cyanosis was graded 3. After five minutes, the second finger of the right hand became red; the others remained cyanotic, graded 2. All the fingers of the left hand had become red except the fifth finger, which was blanched and had a cyanotic tinge. After ten minutes all the fingers of the right hand were bright red, as was also the fourth finger of the left hand. The fifth finger of the left hand suddenly turned an excessively bright red from above downward, and associated with this was a transient rise of temperature above that of the other fingers. At the end of the period of observation there was still a slight trace of cyanosis in the second fingers of both hands. The average temperature of the fingers was 29 C. before immersion; after immersion, 22 C. in the right hand and 26 C. in the left hand.

Spontaneous attacks of blanching occurred when the patient was in the anesthetizing room, the temperature of which was 26.7 C. Both hands were warm at the onset. The temperatures were as follows: R_1, 30.2; R_2, 30.1; R_3, 30.0; R_4, 30.0; R_5, 30.0; L_1, 30.3; L_2, 30.3; L_3, 30.1; L_4, 30.0; L_5, 30.1.

The patient lay on a flat operating table and was covered with a white sheet. Her hands were lying still on the sheet. While she was waiting for the anesthetist she complained that her heart was palpitating and that she felt apprehensive. Suddenly the fingers of both hands became blanched. In order to make accurate observation, the first, second, third and fourth fingers of the left hand only were studied. The second, third and fourth fingers were completely blanched from the onset. A cyanotic tinge of the third finger developed almost immediately. After about a minute, the second and fourth fingers became slightly cyanotic and, together with the third finger, gradually assumed a normal red color, without undergoing obvious hyperemia. The fifth finger appeared to be free from cyanosis and after a few minutes red color gradually crept into the blanched finger from above downward. There was definite hyperemia in this finger, with bright redness and feeling of warmth. It was obvious that the attack was associated with considerable diminution of temperature; both hands felt cold.

After apparent recovery from the spontaneous attack that has been described, ulnar anesthetization, combined with regional infiltration at the base of the fourth and fifth digits of the left hand, was performed. Perfect anesthesia and a marked rise of temperature resulted as follows: L_1, 28.8; L_2, 28.0; L_3, 31.1; L_4, 34.4; L_5, 34.4. The third finger was partially involved in the anesthesia. From 10:30 to 11:00 the left hand was placed in the bipartite water trough; the bases of the fingers were at 15 C. and the terminal phalanges at from 27 to 30 C. When the hand was removed from the trough, the first and second fingers were deeply cyanotic (graded 4); the third finger, of mixed color, and the fourth and fifth, red and completely free from any trace of cyanosis (fig. 2). The temperatures were as follows: L_1, 23.0; L_2, 26.8; L_3, 27.4; L_4, 30.6; L_5, 30.8. When the fingers were tested for analgesia, even a sharp pin prick could not be detected by the unanesthetized fingers. It would appear that tests for analgesia made immediately after long immersion in cold water may be unreliable. Since time is a factor in anesthesia the phase at recovery was not studied, and the patient was taken to an ice chamber that had a temperature of 2 C. The left

hand was now immersed in water at 15 C. from 11:15 to 11:45. When the hand was removed from the water, the first, second and third fingers were deeply cyanotic (graded 4), and the fourth and fifth fingers appeared red. When the fingers were tested for analgesia, it was noted that in the fourth finger, a definite, though slight, tinge of cyanosis was present, which lasted for a few minutes and was replaced by a normal red. This finger was analgesic to pin pricks, as was also the fifth finger; the others had some sensitivity. It was noted, however, that deep pressure could be felt in the fourth finger and not in the fifth; this was true of postural sensibility. There was, therefore, some evidence of diminished efficiency of the local anesthesia, though not until 12:15 did analgesia to pin pricks cease. The temperature of the skin, however, further showed that the anesthesia of the fourth finger was incomplete, whereas that of the fifth finger was still sustained. The temperatures were as follows: At 12 noon, the

Fig. 2 (case 2).—Ulnar anesthetization, combined with regional infiltration at the bases of the fourth and fifth digits, was carried out. Then, for half an hour the hand was placed in a bipartite water trough in which the bases of the fingers were exposed to 15 C. and the terminal phalanges to from 27 to 30 C. The illustration shows an absence of cyanosis in R_5, R_4 and half of R_3.

temperature of L_2 was 28; that of L_4, 30.5, and that of L_5, 33.2. At 12:10 p. m., the temperature of L_2 was 30.5; that of L_4, 33.8, and that of L_5, 34.8. At 12:20 p. m., the temperature of L_2 was 30.6; that of L_4, 33.2 and that of L_5, 34.7. At 12:30 p. m., some degree of postural sensibility and sensibility to deep pressure was present in the fifth finger, but analgesia persisted. There was no trace of cyanosis or blanching of the little finger throughout the experiment.

To show reflex vasoconstriction, the fifth finger (temperature, 29 C.) was placed in water at 15 C. for half an hour; the remaining fingers were in air at a temperature of 26.5 C. and after ten minutes they became cyanotic (graded 1); the cyanosis was deepest in the finger that was immersed in water (graded 3).

Patches of red were present in the fingers not immersed. Throughout the experiment temperatures of the second finger noted at intervals of five or ten minutes were 29.2, 28.4, 27.6 and 26.5 C. On removal from the water, the temperature of the fifth finger was 22.3.

All the fingers were warm (30.2 C.) and of good color. The right hand was placed in water at 38 C. in a room with a temperature of 26 C. With the hand kept under water, the patient was taken into an ice chamber for half an hour. Mild shivering occurred during the last five minutes. The temperature of the water was maintained by the addition of boiling water and was never allowed to fall below 37 C. The patient was then taken from the chamber, and the hand was removed from the water. The whole hand was of a cyanotic tinge, with patches of red. The red returned rapidly. It appeared as if only the arterioles had been sent into spasm. This had been brought about by strong central stimuli which must have overcome the local tendency to vasodilatation.

CASE 3.—A woman, aged 45, had experienced attacks of cyanosis of the hands, brought on by cold or by emotion for two years. This was confirmed by experiment and observation in the hospital. A diagnosis of uncomplicated Raynaud's disease, of two years' duration, was made.

TABLE 3.—*Temperature of Fingers in Degrees Centigrade, Showing Effect of Anesthetization; No Operation* *

Time, a.m.	L_1	L_2	L_3	L_4	L_5
9:30	24.2	24.3	24.3	24.4	24.2
Anesthetization of ulnar nerve and of R_4 and R_5					
10:15	26.8	27.6	29.5	32.3	34.2
Immersion in water for thirty minutes; fingers at 15 C.; remainder of hand at 30 C.					
10:55	22.0	24.0	25.5	25.5	26.0
11:05	25.0	25.5	27.0	27.5	30.8
11:15	31.6	31.4	33.8	33.2	33.6
11:25	32.6	31.4	33.2	32.8	33.4
11:35	31.7	30.9	32.4	32.2	32.7

* The temperature of the room was 25.7 C. This experiment is instructive as showing the potential fallacy of analgesia or relative rise of temperature as an absolute criterion for complete anesthetization.

Special Examinations.—Ulnar anesthetization was combined with infiltration of the base of the fourth and fifth fingers of the left hand. The room temperature was 25.7 C. Following anesthetization there was a considerable rise in temperature (table 3), although that of the fifth finger was greater than that of the fourth. Analgesia appeared to be complete at the beginning of the experiment.

The hand was immersed in the bipartite water compartment; the greater portion of the member was in water at 15 C., and the water in which the terminal phalanges were immersed was at 30 C. When, after thirty minutes, the hand was removed from the water, it was seen that the first and second fingers were deeply cyanotic (graded 4); the third (partially involved in the anesthesia) was cyanotic (graded 2); the fourth, red but with a tinge of cyanosis, and the fifth, red without the slightest trace of cyanosis. After careful note was made of the color and the temperatures, tests for analgesia were made. It was found that there was some return of sensation in the fourth finger, though the analgesia was still complete in the fifth. These observations were in keeping with the higher temperature in the fifth finger and appear to explain the transient cyanosis in the fourth finger. Recovery of color occurred in the remaining fingers within fifteen minutes. Analgesia was deficient in the fifth finger for

thirty minutes after the hand was removed from water, although the temperature was still relatively high. Analgesia was imperfect in forty-five minutes.

CASE 4.—A woman, aged 45, had had a transitory attack of cyanosis of the hands in October, 1928. Further attacks did not occur until March, 1930, since which time several attacks of cyanosis of both hands had occurred with cold or emotion. For the occurrence of cyanosis and simultaneous sweating with emotional disturbance, it was not necessary that the atmosphere be distinctly cold, but cyanosis would not occur in a hot room. Subsequent laboratory observations showed that an emotional stimulus was effective at a room temperature of 25.8 C. There was no definite phase of blanching, and the patient was not certain whether or not a phase of hyperemia occurred, although recovery was usually associated with sensations of heat and tingling.

The patient had had a tendency for many years to have cold hands and feet. As with the hands, the attacks of cold feet had been much more marked in the six months preceding examination. The physician asked her to observe the feet in an attack, and after she had done so she reported that they were bluish,

TABLE 4.—*Temperature of Fingers in Degrees Centigrade, Showing Effect of Anesthetization; No Operation* *

Time, a.m.	R_1	R_2	R_3	R_4	R_5
9:20	26.0	25.6	25.6	25.3	24.9
Anesthetization of ulnar nerve and R_4 and R_5					
9:50	29.0	29.2	31.0	34.1	35.1
Emotional attack with cyanosis					
9:55	26.8	27.2	30.0	33.8	35.0
10:10 Immersion in water for thirty minutes; fingers at 15 C.; remainder of hand at 28 C.					
10:40	21.8	25.8	25.9	26.2	25.9
10:45	24.1	25.8	26.4	25.8	27.8
10:50	25.5	26.8	27.4	29.9	30.5
11:00	26.8	27.0	28.4	31.4	32.5
11:10	29.8	29.0	30.1	31.8	32.2

* The temperature of the room was 25.8 C.

a phenomenon that she had not previously noted. It thus appears that both hands and feet were symmetrically involved; further, over the same period the patient had noticed coldness, without discoloration, of the tip of the nose. On general examination, abnormalities were not discovered; all the palpable vessels were patent, and the blood pressure in millimeters of mercury was 110 systolic and 85 diastolic. The diagnosis was early uncomplicated Raynaud's disease affecting both hands and feet.

Special Examinations.—The left hand was placed in water at 15 C. for twenty minutes, at the end of which time all the fingers were cyanotic (graded 3). The right hand was placed in a bipartite water compartment; the greater part of the hand was in water of 15 C.; the remainder, in water of from 28 to 30 C. The hand was taken out after thirty minutes, and all the fingers were deeply cyanosed (graded 4). The room temperature was 25.9 C.

Ulnar anesthetization was combined with anesthetization at the base of the fourth and fifth fingers of the right hand. The procedure was followed by a sharp rise of temperature in the anesthetized fingers. Just before commencing the tests with cold water, a group of observers entering the room disturbed the patient, and an attack of cyanosis was initiated by the emotional stimulus. The fingers of both hands were involved, with the exception of the anesthetized fingers, which remained of good color throughout. The cyanotic fingers underwent a considerable drop in temperature, but change of temperature in the anesthetized

fingers was inappreciable. The temperature of the fourth finger, however, was slightly less than that of the fifth, and it is possible that anesthetization of the former did not include all the vasomotor fibers in spite of apparent analgesia (table 4). The third finger was partially involved in the anesthesia. After recovery from the psychic attack, the hand was placed in the bipartite water compartment, as in the previous experiment. The hand was removed after thirty minutes. The first, second and third fingers were markedly cyanotic (graded 4), whereas the fourth and fifth fingers were of a good red color, without a tinge of cyanosis. Pulsations were decreased, but still present, in the unanesthetized fingers, but apparently they were absent in the anesthetized fingers. Recovery of amplitude of pulsation was rapid in the anesthetized fingers, but very slow in the remaining fingers. In all the fingers the temperature was reduced to a similar low level, but that of the fourth and fifth fingers rose more rapidly than that of the others. Toward the end of the experiment, analgesia was diminishing, and the temperatures of the fourth and fifth fingers, though maintaining their relatively higher values, did not reach as high a value as before the immersion. No trace of blanching or cyanosis, however, was seen in them.

Case 5.—A woman, aged 40, had had mild symptoms of Raynaud's disease since girlhood, but the condition had beccome more severe in the last few years before examination. When she was at high school, her hands would turn purple, always tended to be cold and clammy and sometimes became swollen in cold weather. Perspiration of the hands was often excessive and uncomfortable. The condition was mild and not very characteristic until the winter of 1926 to 1927, when color reactions in three phases were definitely present: blanching was followed by cyanosis and then by redness. At first the attacks occurred in winter; later (1928), however, they occurred even in summer. Emotion or excitement sometimes caused the hands to turn purple. Immersion in cold water was painful, whether or not changes in color resulted. The feet were always cold, and the patient wore stockings at night. There was no history of changes in color in the lower extremities. The diagnosis was of relatively mild Raynaud's disease of several years' duration.

In view of the progressive nature of the disability, it was decided to perform bilateral cervicothoracic sympathetic ganglionectomy.

Following operation the patient made an uninterrupted recovery, and became completely free from attacks of blanching or cyanosis, in spite of exposure during the winter and frequent immersion of the hands in cold water, which was no longer associated with pain.

Special Examinations One Year After Operation.—After the patient had been in a room that was kept at an almost constant temperature of 23 C. for twenty minutes, the temperatures of the fingers of both hands were taken, with the following results: R_1, 33.8; R_2, 32.4; R_3, 32.1; R_4, 31.7; R_5, 31.7; L_1, 33.8; L_2, 32.3; L_3, 32.6; L_4, 32.4; L_5, 32.3. The color of the fingers was a normal pink.

The right hand was placed in water at 15 C. for twenty minutes. The left hand was placed in a double compartment water bath for thirty minutes. The palms and bases of the fingers of the left hand were surrounded by water at 15 C., and the distal phalanges were in water at 28 C. Throughout the experiment the fingers were seen to be of good color; there was not the slightest trace of cyanosis or blanching. After immersion was ended, the temperatures noted were as follows: R_1, 26.2; R_2, 26.0; R_3, 26.0; R_4, 26.4; R_5, 26.6; L_1, 26.4; L_2, 28.2; L_3, 27.9; L_4, 27.8; L_5, 27.5. At no time in the phase of recovery was there an indication of cyanosis.

The experiments were repeated with an atmospheric temperature of from 0 to 2 C., and again all attempts to produce blanching or cyanosis by exposure to the atmosphere of the ice chamber gave completely negative results. The results of tests for sweating are shown in figure 3.

Tests for sweating showed that there had been complete severance of all sympathetic fibers to the hands.

Case 6.—A woman, aged 20, had begun to have definite changes in the color of the hands two years prior to examination. For the first few months, blanching of the tips of the fingers occurred without cyanosis. Later the phase of blanching was followed by cyanosis. Sometimes cyanosis was present just

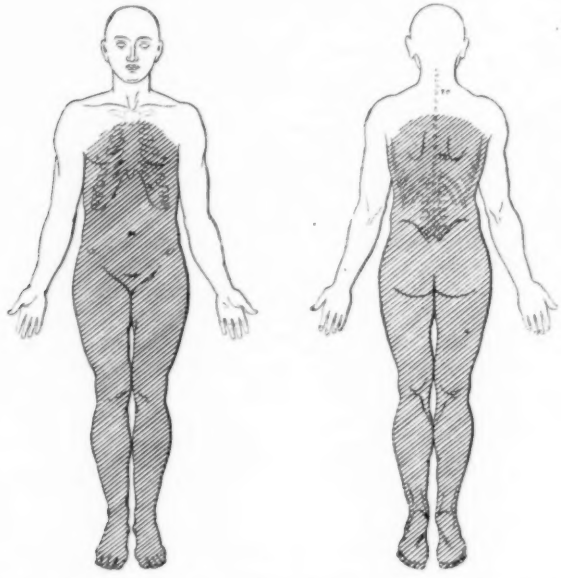

Fig. 3 (case 5).—The hands, arms, face and neck were completely free from perspiration after the patient had been under an electric heater for thirty minutes, following cervicothoracic ganglionectomy.

proximal to the blanching. The phase of redness was not particularly prominent. At the time of examination, cyanosis often occurred without preliminary blanching. At first, the tips of the fingers were involved, but as the disease progressed there was gradual extension proximally as far as the metacarpophalangeal joint.

The initial attacks occurred in winter; later, however, attacks appeared in summer also, particularly in the early mornings and in the evenings, that is, in the cooler parts of the day. Emotion might initiate an attack even on a warm day or in a warm room. Under these circumstances, cyanosis occurred without preliminary blanching. The patient stated that she could easily produce changes in the color by placing her hands or feet in cold water. This was confirmed by us.

Changes in color commenced in the feet the winter following the onset, and the severity and frequency of the attacks that affected the feet increased even more rapidly than those that affected the hands. Blanching and cyanotic phases were definitely present.

The patient stated that after the age of 18 years she was easily fatigued, and that her "nerves were bad." Excitement might cause her to tremble all over. The condition was one of uncomplicated Raynaud's disease, with symptoms of two years' duration.

Operation for Condition of Upper Extremities.—In July, 1929, bilateral cervicothoracic sympathetic ganglionectomy was performed. Immediately after operation, a few blisters that were present on the tips of the fingers of the right hand healed completely. The hands were warm and of good color. It is noteworthy, however, that even while the patient was in the hospital, some blanching of the fourth and third fingers of the right hand occurred on one occasion.

Special Examinations of the Hands After Cervicothoracic Operation.—In the first few months after operation, two or three attacks of blanching of the fingers of the right hand occurred. There appeared to be complete freedom from attacks throughout the winter of 1929 to 1930. The patient was exposed to cold weather, but was careful to wear warm gloves. In the spring of 1930, however, attacks of blanching and cyanosis recurred, affecting all the fingers of the right hand and the second and third fingers of the left hand. The changes in color were seen in the early mornings and in chilly evenings. Immersing the hands in cold water or peeling vegetables would produce an attack. Emotion produced similar attacks in which cyanosis without blanching occurred. The patient stated that the hands were warm and dry, and, in spite of persistent questioning, insisted that she never perspired.

Operation for Condition of the Lower Extremities.—In February, 1930, bilateral lumbar sympathetic ganglionectomy and ramisectomy was performed. Since this operation, the feet had been warm and dry and completely free from changes in color and sweating under any circumstances.

Special Ultimate Examinations of the Hands and Feet.—In September, 1930, the patient returned to the clinic for reexamination. The hands were not particularly warm, but they were of good color and apparently were dry. The temperature of the room was 24.2 C. While the tanks for the water test were being prepared, the patient appeared nervous and expressed apprehension. At the same time there was an attack of cyanosis (graded 1) in the right hand, which affected chiefly the first, second and third fingers. This was associated with a fall of temperature in the fingers of the right hand; hardly any fall in temperature was noticed in the fingers of the left hand, which remained of good color.

The left hand was placed in water at 15 C. for thirty minutes. The right hand was placed in the bipartite water compartment; the greater part of the hand was at a temperature of 15 C., but the terminal phalanges were at from 25 to 30 C. On removing the hands from the water, it was seen that all the fingers of the right hand were cyanotic approximately to the same degree (graded 3). On the left hand, the second and third fingers were also cyanotic, but the cyanosis was of less severity (graded 1) than that of the fingers of the right hand, and the first and fourth fingers had a tinge of cyanosis. All the fingers of the left hand recovered their normal color within eight minutes; those of the right hand remained cyanotic for twenty minutes or longer. The second finger of the right

hand was the first to regain color; blue changed to red from the proximal to the distal portion, and the change was particularly well marked on the ulnar side. Within two minutes, however, this finger became even more cyanosed than previously, indicating secondary spasm of the digital arteries after temporary relaxation. At 11:30 a. m., the fourth finger of the right hand was red; the third finger was less red, with a trace of cyanosis; the first and second fingers were slightly cyanotic (graded 1), and the fifth finger was even more cyanotic (graded 2). The left hand was red. The average temperature of the fingers was 29 C. before immersion; after immersion was ended the temperature of the fingers of the right hand was 26 C. and that of the left hand, 23 C.

The feet were placed in water at 15 C. for thirty minutes. There was a fall of temperature from 33.8 C. to 23.0 C., but not the slightest trace of blanching or cyanosis. Rapid recovery of temperature occurred within fifteen minutes. The room temperature was 26.0 C., but the experiment was repeated in an ice chamber (2 C.) and, subsequently, in water at 10 C. and at 20 C., with similar negative results. Placing the terminal phalanges of the foot in warm water

TABLE 5.—*Temperature of Fingers in Degrees Centigrade One Year After Operation to Determine Presence or Absence of Vasomotor Fibers*

Time, a.m.	R_1	R_2	R_3	R_4	R_5
9:30	30.0	29.6	29.9	29.7	29.5
10:00 Anesthetization of ulnar nerve and R_4 and R_5					
10:30	28.7	28.8	29.8	34.3	34.4
Immersion in water for thirty minutes; fingers at 15 C.; remainder of hand at 26 C.					
11:00	23.5	26.2	26.5	26.4	26.4
11:05	25.6	26.5	26.5	27.5	28.4
11:10	27.4	28.4	28.5	29.2	29.8
11:15	28.8	29.9	29.8	29.9	31.5

after they had been immersed in cold water also gave negative results. This failure to obtain changes in the color of the feet experimentally was in keeping with the patient's own experience.

Experiments on anesthetization were carried out. When the patient entered the room, which was at a temperature of 26 C., the hands were of good color; the readings of temperature are noted in table 5. The patient was then taken to a room the temperature of which was 30.2 C. Ulnar anesthesia combined with regional anesthesia was applied at the bases of the fourth and fifth fingers. The patient rested in the recumbent position for about ten minutes; then the towel covering the hand was removed in order to test for anesthesia. It was then seen that a spontaneous attack of cyanosis had occurred in the first, second and third fingers of the right hand. The anesthetized fingers (fourth and fifth) were bright red, and on gross examination, they seemed warmer than the others. There was no cyanosis of the left hand. The attack probably resulted from the emotional disturbance associated with the injection of the anesthetic. It is of interest that the changes in color took place in a warm atmosphere (30.2 C). The patient immediately returned to the laboratory, which was at a temperature of 26 C., and the temperatures were taken. The temperatures of the anesthetized fingers were 5 degrees higher than those of the other fingers (table 5). The third finger was partly involved in the anesthetization.

The right hand was then placed in the bipartite water compartment; the distal phalanges were then kept at a temperature of 15 C. and the remainder of the hand at from 26 to 28 C. After half an hour, the hand was withdrawn from the

water. The first and second fingers and the radial halves of the middle fingers were markedly cyanosed (graded 4), but the remaining, anesthetized fingers were red. The temperatures of the latter were not elevated, but rose more rapidly than those of the unanesthetized fingers. The cyanosis in the first, second and third fingers lasted for thirty minutes. The observation of the phase of recovery was not prolonged, for there was some suggestion of return of sensation in the fourth finger, and a further experiment in the ice chamber (2 C.) was desired. The hand was immersed for another fifteen minutes in water at 15 C., but though cyanosis returned in the unanesthetized fingers, there was no trace of cyanosis or blanching in the fourth and fifth fingers.

The patient was placed under an electric trough for thirty minutes (fig. 4). The trunk and thighs were covered with large beads of perspiration. On the right forearm there were a few beads of perspiration; similar beads were pres-

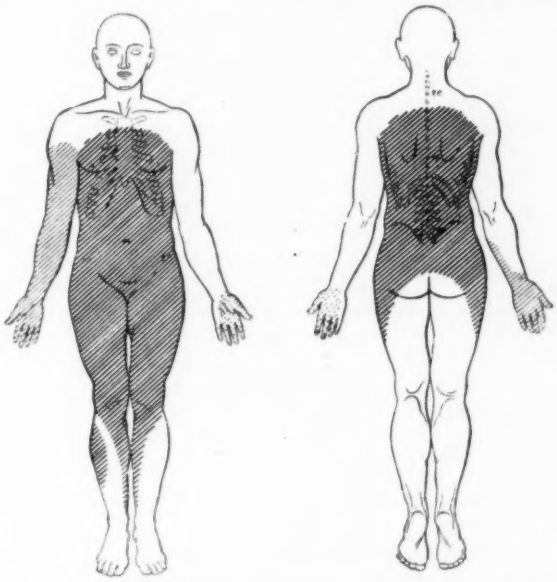

Fig. 4 (case 6).—Areas of freedom from sweating (not shaded) one year and seven months after cervicothoracic and lumbar sympathetic ganglionectomy had been performed.

ent on a small area on the outer side of the right calf and the inner side of the leg. The other parts of the legs and feet were completely dry. The left arm was dry, but slight sweating (graded 2) was present on the first, second and third fingers, and to a less extent (graded 1) on the fourth finger. There was also very slight sweating on the back of the left hand. The head and neck were dry.

This test showed that sweat fibers, and therefore probably vasomotor fibers, were still present in the right upper extremity and to a very slight extent in the left hand. The feet were free from evidence of the presence of sympathetic nerve fibers.

CASE 7.—A woman, aged 31, since the age of 16 years had noticed coldness of the extremities with occasional blanching of the hands, but these phenomena were

almost erased from memory by an attack of polyarthritis which commenced at approximately the same time as that at which the coldness and blanching of the hands was noticed and which persisted for three years. All of the joints were involved at one time or another, including the small joints of the hands. The arthritis disappeared following the administration of vaccine.

Changes in color of the hands had been definitely present for at least thirteen years, and had been more frequent and severe for the last four years before examination. At first, blanching only was present, but later cyanosis occurred without blanching. The phase of rubor was not especially marked. Usually all the fingers of both hands were involved, but sometimes it appeared that only two or three fingers were affected. The attacks were brought on by cold or emotion. In the latter circumstance the atmosphere was sometimes warm.

For about the last ten years before examination, the second and third fingers of the left hand and the second finger of the right hand had been subject to recurring perionychial infection in the winter, with superficial ulceration of the tips of the fingers. On examination, hyperkeratosis was present in these fingers. The

TABLE 6.—*Temperatures of Fingers in Degrees Centigrade Before Operation, Showing Effect of Local and of General Cold* *

Time, a.m.	L_1	L_2	L_3	L_4	L_5
10:15	32.6	32.1	31.8	31.8	32.2
10:45	34.8	35.2	35.4	36.3	35.3
Immersion in water for thirty minutes; fingers at 15 C.; remainder of hand at 30 C.					
11:20	25.7	28.8	28.9	28.8	28.0
Hand in water at 15 C. for thirty minutes; patient in ice chamber at 2 C.					
12:00	19.3	20.2	21.0	20.5	20.0
12:15	26.5	25.7	26.2	25.2	25.8
12:25	33.2	32.6	32.5	32.6	32.3

* The temperature of the room was 32 C.

patient stated that she was nervous; during hospitalization, she appeared to be emotionally unstable; occasional paroxysms of weeping alternated with hilarious laughter.

The diagnosis of Raynaud's disease of marked severity and prolonged duration, complicated by ulceration of three finger tips was made.

Special Examinations Before Operation.—Both hands were immersed in water at 15 C. for thirty minutes; the temperature of the room was 27.2 C. All the fingers of both hands were cyanotic (graded 3) when removed from the water. Recovery of normal color of most of the fingers took place in about fifteen minutes, but the third finger of the left hand remained cyanotic for ten minutes longer. The average temperature of the fingers was 30 C. before immersion and 21 C. after immersion.

The left hand (table 6) was placed in a bipartite water trough; the terminal phalanges were at a temperature of 30 C.; the rest of the hand, at 15 C. The temperature of the room was 27 C. After thirty minutes, the terminal phalanges of all of the fingers were cyanotic; the second, third and fourth fingers were more affected (graded 4) than the others (graded 3). The average temperature of the fingers was 30 C. before immersion and 27 C. after immersion.

Experiments on anesthetization were carried out under unfavorable circumstances on an unusually warm day; the temperature of the room was 32 C., and it could not be reduced within the time limit of the experiment. These circum-

stances do not vitiate the positive results obtained, which were confirmed by extending the experiment in the atmosphere of an ice chamber at 0 C. Since in the previous experiments the third finger of the left hand had appeared to be affected most, block anesthesia was induced at its base, the contiguous sides of adjacent fingers receiving some anesthesia. The effect of the anesthesia on surface temperature could not be analyzed, for there was a rise in temperature of all fingers owing to the warm atmosphere. The hand was placed in the bipartite water trough for thirty minutes; the distal phalanges were at 30 C., and the proximal part of the hand, at 15 C. As was anticipated from the preliminary experiments, the unanesthetized fingers became cyanotic (graded 3), but the middle finger also had a definite tinge of cyanosis.

The patient was then taken to an ice chamber, and the same hand was immersed in water at 15 C. for thirty minutes. Definite cyanosis (graded 2) was present in the anesthetized middle finger, though it was less than that in the unanesthetized fingers.

TABLE 7.—*Temperatures of Fingers in Degrees Centigrade, Showing Effects of Local Cold*

Time, a.m.	R_1	R_2	R_3	R_4	R_5
9:30	30.4	30.4	30.4	30.3	30.2
Hand immersed in water at 15 C. for thirty minutes					
10:05	22.0	21.4	21.6	21.4	21.0
10:10	23.6	23.3	23.8	23.6	23.8
10:17	25.0	23.5	23.8	23.9	23.9
10:25	25.6	25.1	25.0	25.2	25.2
10:35	28.8	28.5	28.5	28.3	28.0
11:00	29.8	29.5	29.4	29.4	29.6
	L_1	L_2	L_3	L_4	L_5
11:15	30.8	30.1	30.2	30.0	30.0
11:20 to 11:50 Immersion in water for thirty minutes; fingers at 15 C.; remainder of hand at 30 C.					
Time, p.m.					
12:05	24.8	26.2	26.5	26.5	25.5

In this case the effect of fever caused by the intravenous administration of vaccine is of great significance, as it gives evidence of some organic change in the digital arteries of the fingers that were subject to previous trophic changes. These were the second finger of the right hand and the second and third fingers of the left hand. In these digits the surface temperatures at the height of fever were approximately 1 degree less than those of the remaining fingers. The temperatures were as follows: R_1, 34.9; R_2, 33.7; R_3, 34.7; R_4, 34.7; R_5, 35.0; L_1, 34.9; L_2, 33.6; L_3, 33.8; L_4, 34.4; L_5, 34.8. The temperature of the room was 25.6 C. Bilateral cervicothoracic sympathetic ganglionectomy was performed

Special Examinations After Operation.—Three weeks after operation, the left hand was placed in a bipartite water trough for thirty minutes (table 7). The terminal phalanges were at a temperature of 30 C. and the rest of the hand, at 15 C. On removing the hand from the trough, the terminal phalanges of the second and third fingers were found to be cyanotic (graded 2); the terminal phalanges of the remaining fingers were a good red. The temperature of the room was 23.3 C. Within a few minutes the cyanotic color of the second and third fingers was replaced by a dusky red color, which persisted for about twenty minutes.

The right hand was placed in water at 15 C. for thirty minutes. At the end of this time all the fingers were a good red except the second finger, which was

cyanotic in its distal half for five minutes and of a dusky red for twenty minutes longer. Elevation of the hand just after its withdrawal from the water produced blanching of the terminal phalanx of this finger; dependency increased the intensity of the cyanosis.

The patient was placed under an electric heater (with twelve lights) that covered the entire body and limbs, excluding the face. After thirty minutes the heater was removed and the region of sweating was demarcated by cobalt blue. There was complete absence of sweating of the arms. The face was free from perspiration except for a small area over the right cheek and the right side of the forehead. The rest of the body was freely covered with perspiration. The experiment showed that the sympathetic nerves to the hands had probably been completely interrupted.

In advanced cases the diseased digital arteries may remain hypersensitive to cold after operation.

TABLE 8.—*Postoperative Studies of Temperature of Fingers in Degrees Centigrade, Showing Effects of Local and General Cold* *

Time, a.m.	R_1	R_2	R_3	R_4	R_5	L_1	L_2	L_3	L_4	L_5
9:00	36.1	33.6	33.4	33.4	33.5	33.4	33.7	33.2	33.1	33.6
9:08 to 9:28	Hand immersed in water at 15 C.					Immersion in water: fingers at 15 C.; remainder of hand at 30 C.				
9:30	26.0	22.8	22.8	22.9	22.9	23.6	26.0	26.0	26.7	26.1
9:35	27.4	25.0	25.2	29.0	29.8	30.5	29.0	28.7	29.5	29.3
9:40	29.3	26.5	27.5	30.5	30.6	31.4	30.5	29.5	30.9	30.6
9:45	30.2	27.7	28.3	31.2	31.8	32.0	31.5	30.5	32.0	31.9
9:52	31.6	29.9	30.9	32.2	32.5	33.0	33.2	32.0	33.4	33.5
10:00	33.5	31.8	32.0	33.0	33.6					
9:00	....	31.6	31.4	31.8	31.5	....	31.6	31.6	31.6	31.4
9:05 to 9:20	Patient exposed to air in ice chamber at 0.2 C.					Hand in water at 15 C.; patient in ice chamber at 2 C.				
9:23	....	....	....	....	....	....	19.2	19.3	19.6	19.4
9:26	....	24.2	25.6	26.4	26.0	....	20.1	20.8	22.2	21.9

* The atmospheric temperature, exclusive of that of ice chamber, was 26 C.

CASE 8.—A woman, aged 45, had a moderately severe case of Raynaud's disease of five years' duration, with ulceration of the second and third fingers of both hands. An emotional upset, or exposure to cold, produced blanching of the fingers. In the later stages of the disease cyanosis followed blanching; the latter sometimes did not develop. Ulceration was associated with hard, white concretions at the finger tips. Incisions for drainage of pus had been necessary. The feet were affected at the same time but to a less extent, and they were without ulceration.

Special Examinations Before Operation.—At a room temperature of 25.6 C., immersion of the hands in water at 15 C. produced blanching and cyanosis in all fingers. The average temperature of the fingers was 28 C. before and 21 C. after immersion. Further results were obtained in the ice chamber at a temperature of 0.2 C.; the left hand was placed in cold water and the right exposed to the cold air of the chamber. Anesthetization was not done. Bilateral cervicothoracic sympathetic ganglionectomy was performed.

Special Examinations After Operation.—Three weeks after operation, with the room at a temperature of 26 C. (table 8), the right hand was placed in water at 15 C. and the left hand in the bipartite compartment; the terminal phalanges were at temperatures of from 27 to 30 C., and the proximal portion of the hand was at a temperature of 18 C. The hands were immersed in water for twenty minutes, but

blanching or cyanosis did not develop. It will be noticed from the tables, however, that the temperatures of the second and third fingers of the right hand lagged in rate of recovery (fig. 5). A similar phenomenon was not so obvious in the left hand, for the terminal phalanges were kept in relatively warm water. In spite of the absence of changes in color, therefore, there was evidence of abnormal behavior of the ulcerated fingers.

The next day the patient was taken to the ice chamber the temperature of which was 2 C.; the left hand was placed in water at 15 C. for fifteen minutes, and the right hand was exposed to the air. Slight cyanosis was produced in the second and third fingers of the left hand, and blanching, with traces of cyanosis, in the second finger of the right hand. There was no change in color of the remaining fingers. After the patient entered the adjoining room, the temperature of which was 25.6 C., the fingers regained their normal color within five minutes. However, records of temperature (table 8), though not complete, gave evidence of

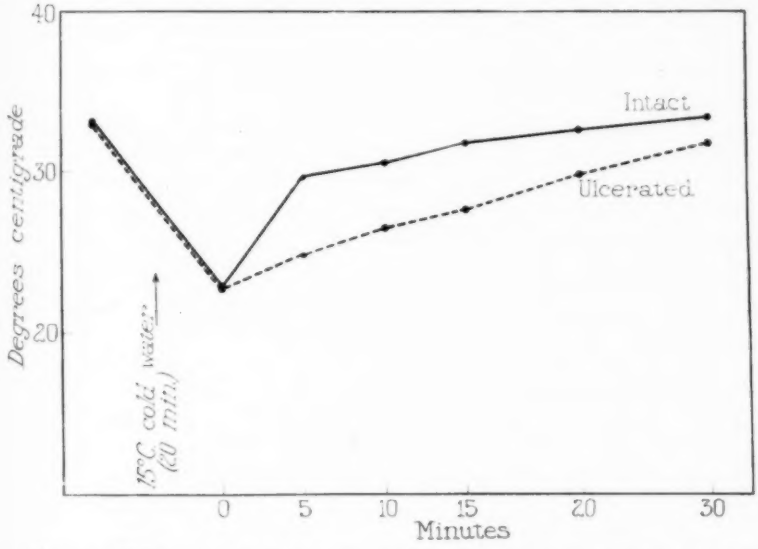

Fig. 5.—Differences in the recovery of surface temperature by intact and by ulcerated fingers, after exposure to cold. These values were obtained after cervicothoracic sympathectomy had been done.

the same lagging in recovery of the affected fingers as in the previous experiment. It was thus proved that manifestation of abnormal behavior of the vessels could be produced in the ulcerated fingers after cervicothoracic sympathectomy.

Tests for sweating showed complete absence of perspiration in the arms. It is concluded, therefore, that there were no intact sympathetic fibers after the operation but that in severe, complicated cases the arteries may react abnormally apart from nervous influences.

CASE 9.—A woman, aged 30, was first seen in January, 1924. There were no previous illnesses except a vague history of "heart trouble." The patient had had a tendency to have cold hands and feet and had had chilblains as long as she could remember, but there was a definite history of numbness and of some changes in color in the hands since the age of 16 years. The fingers became cold, blue and

painful, especially the second and third fingers of the right hand, which the patient believed were affected earliest. At times the cyanosis appeared to have been preceded by blanching, but the patient's memory was uncertain on this point. The fingers and remaining part of the hands would also swell in cold weather, the skin becoming stretched and glossy. At first these attacks occurred only in winter, but subsequently they occurred in summer also. Excitement and emotion would produce attacks unless the weather was excessively warm. The hands actually became frozen four years before examination. In June, 1926, it was noted that during the last few months the hands had been almost constantly blue, cold and painful.

The feet were affected about the same time as the hands. They became blanched and cyanotic, and were more painful than the upper extremities. The nose tended to become cold, but changes in color were not noted.

On examination in 1924, the hands were cold, clammy and swollen, and the feet were cold. The history of changes in color in the hands and feet was corroborated by observation in the hospital. It was noted at the time that the patient was of an asthenic type with a constitutional inferiority.

The case was one of severe Raynaud's disease, of many years' duration, without ulceration of the finger tips. Both hands and feet were affected.

Treatment and General Progress.—In November, 1925, bilateral lumbar sympathetic ganglionectomy was performed. Following operation, the feet became very warm and dry and have persistently maintained a high temperature, about 35 C., ever since. There has never been the slightest trace of cyanosis, blanching or sweating of the feet since the operation, and it will be seen from the experiments that this remained true under the most extreme and varied local and general conditions that could be devised. Further tests showed that reflex sweating could not be produced in the feet under any circumstances, indicating that all sweat fibers and vasoconstrictor fibers had been completely removed.

In 1926, bilateral cervical sympathetic ganglionectomy through the anterior approach, combined with bilateral brachial periarterial sympathectomy, was performed. For the first few days after operation, that is, for the febrile and postanesthetic period, the result appeared to be perfect; the hands were warm and pink. But on the third day it was noted that the left hand was warmer than the right, and on the fifth day the right hand was moist and there were attacks of cyanosis which were most marked in the second finger. One month later it was noted that both hands were moist, the right more than the left. Subsequently, attacks of cyanosis occurred, more in the right hand than in the left, though both hands were involved. The presence of perspiration indicated that some sympathetic nerve fibers were still intact, more on the right side than the left. The condition gradually became worse, and in November, 1928, bilateral thoracic sympathetic ganglionectomy and ramisectomy was performed by the posterior approach. The procedure appeared to offer some technical difficulties owing to the previous operation.

The immediate results of the second operation for relief from the condition of the hands appeared to be excellent. The hands became warm and dry, and the patient was free from attacks of cyanosis throughout that winter.

In April, 1929, changes in color appeared in the hands, and attacks had persisted ever since. Both hands were involved, the right much more severely than the left. The attacks in the left hand were often almost negligible, but occasionally were of moderate severity. In the right hand the second and third fingers were most affected; the first, next in order of severity, and the fourth and fifth fingers, least. The frequency and severity of attacks progressed for a few months

and then became fairly stationary. Cold and emotion were the exciting factors; the latter was effective even in a warm room, but not when it was excessively warm.

In May, 1929, the patient noticed sweating of the hands for the first time since the operation of 1928. An area on the dorsum of the right hand proximal to the second finger was affected. At first this condition was localized, but in the next few weeks it gradually spread to the whole length of the second finger, and subsequently the third finger and fourth finger were involved. Subjectively, the fifth finger appeared to be free from sweating. The patient had also noted very slight sweating on the left hand, but in view of the small amount of it she was not aware of how many, or in what order, fingers had become affected.

The patient believed that there was some relationship between the progress of the severity of the recurring attacks of cyanosis and of the sweating. The latent period and progressive return of symptoms suggest the possibility of regeneration of nerve fibers. With the usual uncomplicated ganglionectomy, it is difficult to imagine that such regeneration could take place.

TABLE 9.—*Temperatures in Degrees Centigrade of Fingers in a Spontaneous Attack of Cyanosis After Incomplete Cervicothoracic Sympathetic Ganglionectomy* *

Time, a.m.	R_1	R_2	R_3	R_4	R_5	L_1	L_2	L_3	L_4	L_5
9:50	26.7	26.5	26.5	26.6	26.7	28.4	28.2	28.2	28.3	27.9
10:00	27.3	27.2	26.8	26.8	27.0	28.8	28.7	28.6	28.4	28.0
10:10	27.4	27.1	27.0	27.0	27.2	29.0	28.5	28.3	28.3	28.6
10:20	27.9	27.7	27.6	27.9	28.0	29.3	29.2	29.1	29.0	28.8
10:30	28.7	28.7	28.6	28.6	28.7	29.1	28.9	28.9	28.9	28.9

* The temperature of the room was 25 C.

Special Examinations After Operations.—The patient entered a room (temperature 25 C.) for observation at 9:45 a. m., having come from the street (temperature 24.2 C.). The fingers of the right hand were cyanotic; the cyanosis of the third finger was graded 4; that of the first and second, 2, and the fourth and fifth fingers were dusky red with bluish patches. On gross examination, cyanosis was not perceived in the left hand. The temperature of the fingers of the right hand was higher than that of the left (table 9). Recovery of color took place in about twenty minutes. Elevation of the hand decreased, and dependency increased, the intensity of cyanosis.

The right hand, which was a good red, was put into water at 15 C. for twenty minutes; the temperature of the room was 26.7 C. When the hand was removed from the water, all the fingers were cyanosed; the third finger had the deepest color (graded 4), and the fifth finger was of only a dusky red, with a cyanotic tinge. Its normal temperature was recovered slightly more rapidly than that of the other fingers. Cyanosis of all fingers had almost disappeared within ten minutes (table 10).

The right hand was placed in the bipartite trough, in which the water was at a temperature of 15 C.; the terminal phalanges were at a temperature of 30 C. The temperature of the room was 25.4 C. After thirty minutes the hand was removed from the water, and all the fingers were seen to be deeply cyanotic (graded 4). After five minutes had elapsed, the fifth finger turned red, but the other fingers remained deeply cyanotic. Within another few minutes the ulnar side of the fourth finger turned red; the radial side and the outer three fingers retained their cyanotic color for about twenty minutes longer.

Ulnar anesthetization was not suitable for the right hand, for the fifth finger was the least affected. When the patient entered the room, which was at a temperature of 25 C., the fingers of the right hand were cyanotic; cyanosis of the second and third fingers was deepest. Local anesthetization at the base of the middle finger was commenced at 9:20 a. m. Within a few minutes the proximal and middle phalanges and the adjacent portion of the distal phalanx became analgesic on the palmar aspect, and cyanosis disappeared from the corresponding area. Supplementary local anesthesia applied to the third finger produced complete disappearance of cyanosis and a small rise of temperature (table 11) in that

TABLE 10.—*Temperatures in Degrees Centigrade Before and After Immersion in Cold Water of Fingers of Hand Which Had Undergone Spontaneous Attacks of Cyanosis but Which Had Recovered* *

Time, p.m.	R_1	R_2	R_3	R_4	R_5
3:05	30.7	30.8	30.6	30.5	30.7
Immersion in water at 15 C. for twenty minutes					
3:40	26.0	24.2	24.4	26.2	27.0
3:48	30.6	29.4	29.2	29.4	30.2
4:10	32.4	32.0	32.0	32.3	32.4

* The temperature of the room was 26.7 C.

TABLE 11.—*Temperature of Fingers of Hand After Operation, Showing Effect of Anesthetization* *

Time, a.m.	R_1	R_2	R_3	R_4	R_5
9:10	25.5	25.2	25.2	25.0	25.3
Anesthetization of R_3					
9:30	25.6	25.2	26.4	24.8	24.8
9:40	27.4	27.2	28.2	27.0	26.7
Immersion in water at 15 C. for fifteen minutes					
10:00	22.6	22.6	22.8	22.4	22.0
10:10	25.2	24.8	25.2	24.5	24.2
10:15	25.6	25.6	26.0	25.4	25.2
10:25	27.0	26.9	28.0	27.0	26.4
10:35	28.1	28.0	29.4	28.1	28.0

* The temperature of the room was 26.7 C.

finger. Although cyanosis persisted in the remaining fingers, it was diminishing. The concomitant partial spontaneous recovery obscured to some extent the rise of temperature in the third finger. When all the fingers had recovered their color five minutes later, the hand was immediately plunged into water at 15 C. for fifteen minutes. The studies before immersion were curtailed, for we were somewhat uncertain as to the probable duration of anesthesia.

On removal from the cold water, the hand presented a striking appearance; the entire hand, as far as the wrist, was deeply cyanosed except for the anesthetized third finger, which was red and which was without any tinge of cyanosis or blanching. The remaining fingers recovered their color in thirty minutes, but the third finger remained red.

In an endeavor to show the experimental result to others interested, the study of recovery was curtailed; the patient was given three glasses of ice cold water to drink, and then was taken to another building. On arrival, it was observed that cyanosis had returned to all the fingers except the anesthetized third finger, which had persistently maintained a good color throughout the experiment.

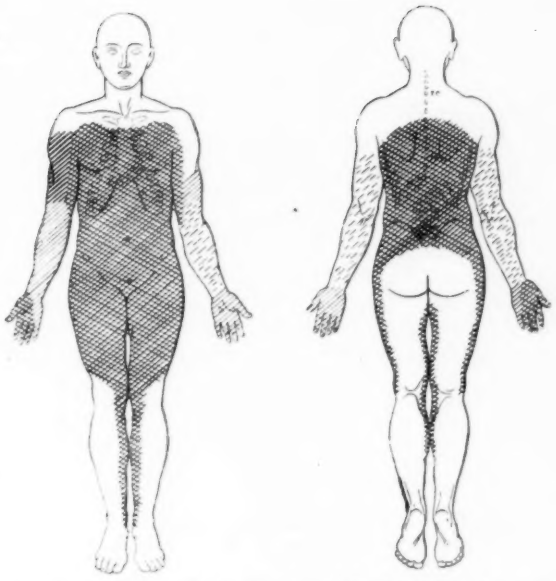

Fig. 6 (case 9).—Presence of sweating (shaded) of the upper extremities after cervicothoracic sympathetic ganlionectomy, indicating persistence of the fibers. The absence of sweating (unshaded) in feet indicates an absence of fibers after lumbar sympathetic ganglionectomy done five years previously.

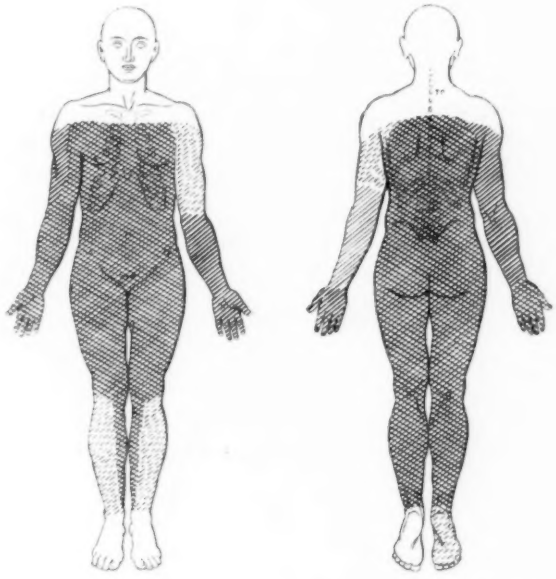

Fig. 7 (case 9).—Areas of sweating (shaded) after the administration of pilocarpine in same patient as that represented in figure 6. The absence of sweating in the unshaded areas is evidence of atrophy of the sweat glands.

The studies of temperature do not permit us to conclude that there was full relaxation of the digital arteries of the third fingers in spite of the red color. In this case anesthetization was carried out at the base of the proximal phalanx, a method subsequently discarded as inefficient. Therefore the interpretation of the limited rise of temperature is that there was imperfect anesthetization, or perhaps abnormal response of the artery in spite of anesthetization; the latter is possible in view of the severity and prolonged course of the disease in this case.

The feet were at first immersed in water at 15 C. for thirty minutes; the temperature of the room was 24 C. Neither cyanosis nor blanching could be detected at any period of this experiment. The terminal phalanges of the right foot were then placed in water at a temperature of 32 C. in an effort to produce cyanotic discoloration, without success. The tests were repeated in an ice chamber at 0.5 C., with similar negative results. Similar tests subsequently were carried out on the feet, with water of different temperatures and with varying time of immersion, but no trace of blanching or cyanosis could be produced. This confirmed the patient's own experience (table 12).

TABLE 12.—*Temperature of Toes About Five Years After Operation, Showing Effects of Differential Local Temperatures**

Time, a.m.	R_1	R_2	R_3	R_4	R_5	L_1	L_2	L_3	L_4	L_5
9:30	35.3	34.6	34.6	34.8	35.2	36.0	35.2	35.8	35.8	36.0
Immersion in water at 15 C. for thirty minutes										
10:00	21.5	21.4	21.6	21.4	21.2	22.1	21.5	21.9	22.0	21.9
Immersion in water at 32 C. for five minutes										
10:10	29.4	29.8	29.7	29.9	30.0	26.7	26.5	25.9	25.9	25.9

* The temperature of the room was 24 C.

The patient was placed under a full-length electric heater for thirty minutes. Sweating was detected by cobalt blue filter paper. Perspiration was not present over the legs below the knee, except on the inner side of the leg. The feet remained perfectly dry. The head and neck were free from sweat. The trunk perspired most profusely. There was a moderate degree of sweating on the right arm and a marked degree on all fingers except the first. There was little sweat on the left arm, but sweat was definitely present on the left hand, although the amount was small. The distribution and degree of sweating corresponded approximately with the tendency of the arteries to enter into spasm (fig. 6). A hypodermic injection of ⅙ (0.01 Gm.) grain of pilocarpine produced sweating in the same areas as those in which heating produced it with downward extension in the lower limbs. This was especially noticeable posteriorly on the buttocks, thighs and calves. Pilocarpine probably acted directly on the sweat glands that had not completely degenerated in these areas, though there was no evidence that any remained in a functional state on the head and neck. The test with pilocarpine is no indication of the distribution of nerve fibers (fig. 7).

THE CEREBRAL CIRCULATION

XIV. THE RESPIRATORY QUOTIENT OF THE BRAIN AND OF THE EXTREMITIES IN MAN *

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Observations on the respiratory quotient of the brain in living unanesthetized persons have not been reported. It is possible to calculate the respiratory quotient of a portion of the body, as Doisy and Beckmann [1] pointed out, by dividing the increase in the carbon dioxide content of the venous blood by the decrease in its oxygen content, with reference to the carbon dioxide and oxygen content of arterial blood. The demonstration of Myerson, Halloran and Hirsch [2] that blood may be obtained safely and without undue pain from the internal jugular vein presents an opportunity for measuring the respiratory quotient of the brain in man. We are indebted to Meyerson and his associates for demonstrating the technic of making jugular punctures. The blood contained in the vein at the point of puncture, opposite the tip of the mastoid, comes from the brain. Though there are anastomoses through the cranium with branches of the external jugular vein, e. g., through the orbit, the two systems are largely independent; this is shown by the striking difference in the gaseous content of blood taken from the external and internal jugular veins.

I have published observations [3] concerning fifty-one occasions on which blood was taken from an artery, an internal jugular vein and a cubital vein; in these instances the average respiratory quotient was 0.90 for the brain and 0.84 for the arm. In forty cases, the average quotient based on measurements of blood taken from an external jugular vein was 1.2. Because this blood was nearly arterial in its gaseous content, the value as stated is open to doubt.

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* From the Department of Neuropathology, Harvard Medical School, and the Thorndike Memorial Laboratory, Boston City, Hospital.

1. Doisy, E. A., and Beckmann, J. W.: The Relation Existing Between Arterial and Venous Blood of the Dog with Special Reference to the Plasma Chlorides, J. Biol. Chem. **54**:683 (Dec.) 1922.

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3. Lennox, W. G.: The Oxygen and Carbon Dioxide Content of Blood from the Internal Jugular and Other Veins, Arch. Int. Med. **46**:630 (Oct.) 1930.

There are considerations that limit the accuracy of the respiratory quotient calculated in this manner in an individual case or in a small series of cases. Alterations of the carbon dioxide content of the blood may be due, not to changes in tissue metabolism, but to variations in the depth of respiration, in the acid-base composition of the blood or in the rate of diffusion of carbon dioxide through the skin.

The degree of distortion of the respiratory quotient that follows artificial variation in the composition of alveolar air is shown in the following experiments. In twelve instances, the tension of carbon dioxide in the lungs was reduced by having subjects overventilate vigorously; in twelve instances, subjects breathed air either rich or poor in oxygen which contained from 5 to 10 per cent of carbon dioxide; in fifteen experiments, subjects breathed air either normal or

TABLE 1.—*Average Changes in Arterial Blood and in Respiratory Quotients Resulting from Variations in the Gaseous Content of Alveolar Air*

	Change in Arterial Blood		Respiratory Quotient			
			Brain		Leg	
Procedure	Oxygen Content, per Cent by Volume	Carbon Dioxide Content, per Cent by Volume	Before	During	Before	During
Hyperpnea	—0.4	—11.8	0.83	1.19	0.73	2.21
Breathing high carbon dioxide	—0.2	— 2.3	1.00	1.21	0.87	0.54
Breathing low carbon dioxide	—3.9	— 4.4	0.95	1.18	0.71	2.70

rich in carbon dioxide but poor in oxygen. Table 1 shows the average changes in the gaseous content of arterial blood that resulted and the average respiratory quotients before and during the procedure, both in the brain and in the leg. It will be seen that these procedures produced great distortion of respiratory quotients. Such distortions were greater in blood passing through the brain, and the variations from the respiratory quotient obtained under normal conditions were not necessarily in the same direction in the brain and in the leg. For this reason we shall report results in a large series of cases, in which the average findings differed somewhat from those in the previously reported smaller series. We also have obtained data that permit calculation of the respiratory quotient for the leg.

MATERIALS AND METHODS

The persons used for these observations, who were for the most part epileptic, were patients in the neurologic service of the Boston City Hospital. Those with abnormal pulmonary or cardiac conditions or with fever were excluded. A few were used on several occasions. Subjects were required to lie quietly for half an hour before blood was withdrawn. Samples were secured without the use of

stasis, and after the skin over the vein had been anesthetized by means of procaine hydrochloride, the blood was taken without exposure to air, and the gases were measured at once in the apparatus and by the method described by Van Slyke.[4]

RESULTS AND COMMENT

On 120 occasions, blood was obtained from an artery and an internal jugular vein. The average measurements of blood gases are displayed in table 2 and in the accompanying chart. The average difference in the oxygen content of blood from the arterial and the internal jugular vessels (the A-V difference) was 6.2 per cent by volume. The difference in the carbon dioxide content was 5.82 per cent by volume, representing a respiratory quotient of 0.95. This figure is higher than the 0.90 that we reported previously in the group of

TABLE 2.—*Average Measurements of Gases and of Dextrose in the Blood from an Artery and from the Internal Jugular, Cubital and Femoral Veins* *

		Artery, per Cent by Volume			Vein, per Cent by Volume				Dextrose			
Vein Used	Number of Cases	Oxygen Content	Oxygen Capacity	Carbon Dioxide Content	Oxygen Content	Oxygen Capacity	Carbon Dioxide Content	Respiratory Quotient	Number of Cases	Artery, Mg. per 100 Cc.	Vein, Mg. per 100 Cc.	Difference, Mg. per 100 Cc.
Internal jugular...	120	18.12	19.56	49.14	11.96	19.2	54.96	0.95	39	99	90	9
Cubital.....	100	18.48	20.11	48.12	12.80	19.7	53.01	0.86	39	96	91	5
Femoral....	75	17.99	19.36	49.62	13.44	....	52.99	0.72	22	101	97	4

* See also accompanying chart.

fifty-one persons. The difference can be explained by the fact that in the present series several cases with meningitis and very low quotients were excluded. Also the jugular punctures were performed more easily in the more recent cases. We regard the value 0.95 as the more nearly correct.

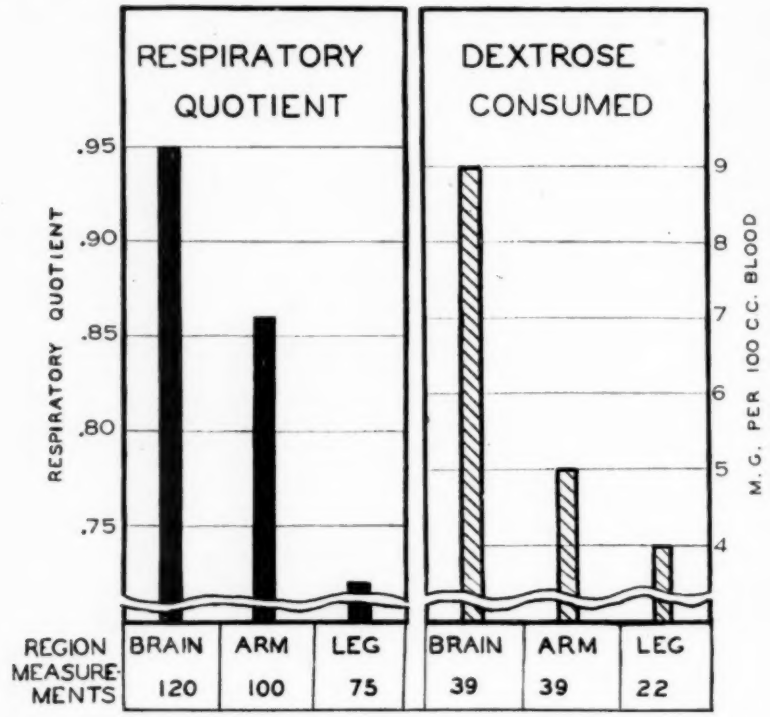
On using much the same procedure, Himwich and Nahum [5] obtained an average value of 1 in a small group of anesthetized dogs. Loebel,[6] using the apparatus of Warburg, reported 0.86 as the respiratory quotient of the brains of two rats.

4. Van Slyke, D. D.: Portable Form of Manometric Gas Apparatus and Certain Points in Technique of Its Use, J. Biol. Chem. **73**:121 (May) 1927. Samples of blood were not taken simultaneously from the different vessels; the order used was chosen at random. Arterial blood was taken from a brachial, radial or femoral artery.

5. Himwich, H. E., and Nahum, L. H.: Respiratory Quotient of the Brain, Proc. Soc. Exper. Biol. & Med. **26**:496, 1929.

6. Loebel, R. O.: Beitrag zur Atmung und Glykolyse tierischer Gewebe, Biochem. Ztschr. **161**:219, 1925.

There has been a difference of opinion as to whether the metabolism of various foodstuffs (and therefore the respiratory quotient) is uniform for different portions and tissues of the body. The experiments of Himwich and Castle [7] indicate that the respiratory quotient of muscles is not the same as that of the whole body. We did not obtain the respiratory quotient of our patients, but because they were eating a usual diet and gave no evidence of an increased metabolic ratio, observations being made from four to fifteen hours after the ingestion of



The left hand portion represents values for the respiratory quotients; the right hand portion, the milligrams of dextrose per hundred cubic centimeters of blood that disappeared from the blood in its passage through the tissues. The figures at the bottom indicate the number of observations.

food, there is no reason to suppose that the total respiratory quotient varied significantly from the usual 0.82. If the respiratory quotient for the brain is 0.95, it is obvious that certain other portions of the body must have a lower than average rate.

7. Himwich, H. E., and Castle, W. B.: Studies in the Metabolism of Muscle: I. The Respiratory Quotient of Resting Muscle, Am. J. Physiol. **83**:92 (Dec.) 1927.

On a hundred occasions (using the same general group of patients) blood was taken from a vein in the elbow. The average difference between arterial and this venous blood was 5.68 per cent by volume for oxygen, and 4.89 per cent by volume for carbon dioxide, giving a respiratory quotient of 0.86.

The tissues drained by the superficial veins of the arm are mostly skin and subcutaneous tissues. The femoral vein, on the other hand, drains the large muscles of the leg. In seventy-five instances in which blood was taken from an internal jugular vein, we obtained blood also from a femoral vein. In these seventy-five cases, the average difference between arterial and femoral venous blood was 4.55 per cent by volume for oxygen and 3.37 per cent by volume for carbon dioxide, giving a respiratory quotient of 0.72.

It is difficult to account for the great differences in the respiratory quotients of the arm and the leg, except on the basis of a difference in the tissues through which the blood had traveled. It would appear from these observations that muscular tissue has a lower respiratory quotient than either the brain or the skin. As the latter tissues are ectodermal in origin, it is not illogical that their metabolism should be similar.

Our data on this point are in general agreement with those of Himwich and Castle,[7] who in dogs observed an average respiratory quotient of 0.77 for the intact leg and 0.71 for the muscles of the leg alone.

In our series one observes that the venous blood from the brain (which is most reduced) represents the highest quotient, and the blood from the leg (which is least reduced), the lowest. This relationship, however, is not consistent, for blood from the external jugular vein, the oxygen content of which was only 1.4 per cent by volume less than that of arterial blood, represents the highest respiratory quotient (1.2).

The relatively high respiratory quotient of the brain suggests that the metabolism of nerve tissues involves a larger use of carbohydrates than is the case with muscles. Meyerson and Halloran[8] measured the dextrose in the venous blood of a large series of psychotic patients and obtained distinctly low values in blood that had passed through the brain, in contrast with blood that had passed through the arm. In thirty-nine of our patients in whom measurements of blood sugar were made, the difference between arterial and venous blood was 9 mg. for blood leaving the brain and 5 mg. per hundred cubic centimeters for blood leaving the arm, while in a smaller group of twenty-two cases it was 4 mg. for blood leaving the leg. These differences in the consumption of sugar in a rough way parallel differences in respiratory

8. Myerson, A., and Halloran, R. D.: Personal communication to the authors.

quotients. However, they also parallel differences in the oxygen consumed from the blood, and they may therefore reflect simply a relatively slow flow of blood through the brain. As measurements of the flow of blood or of the metabolic rate of the tissues are lacking, we are unable to relate the high utilization of sugar of the brain with its high respiratory quotient.

The values for respiratory quotients that have been named are uncorrected. Himwich and Castle[7] devised a formula whereby correction is made for differences in the concentration of arterial and venous blood. Because we did not measure the oxygen capacity of many of the samples of blood from the femoral vein, we were unable to make correction for the respiratory quotient of the leg. We measured the oxygen capacity of 120 samples of arterial blood and approximately 250 samples of venous blood. The arterial blood had an average oxygen capacity that was 0.4 per cent by volume greater than that of venous blood, indicating a slight dilution of the blood in its passage through the tissues. Correction for this difference in concentration reduces the stated respiratory quotients by less than 0.005, an amount insufficient to alter the values presented.

SUMMARY

The respiratory quotients of these subjects were calculated by comparing the oxygen and carbon dioxide content of blood drawn from an artery with that of blood drawn from an internal jugular vein (one hundred and twenty occasions), from a superficial vein of the arm (one hundred occasions) and from a femoral vein (seventy-five occasions).

The average respiratory quotients of the portions of the body represented differed widely, that of the brain being 0.95, that of the arm 0.86, and that of the leg, 0.72.

The observations indicate that the respiratory quotient of certain ectodermal tissues (brain and skin) is higher than that of muscles.

More dextrose disappears from the blood in its passage through the brain than in its passage through the extremities.

THE CEREBRAL CIRCULATION

XV. THE EFFECT OF MENTAL WORK *

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The response of the circulatory system to muscular work has been studied extensively. The effect of mental exertion on the intracranial circulation has received little attention because of the obvious difficulty of observing changes in the flow of blood through the brain of man.

By means of experiments with animals, many facts of importance concerning the intracranial circulation have been uncovered. For example, the extensive studies of Forbes and his co-workers [1] have demonstrated that the arterioles of the pia can be made to dilate and constrict in response to stimulation of the vagus or sympathetic nerve or to alterations in the chemical constituents of the blood. Stimulation of cranial nerves also seems to be effective. Alexander [2] threw a strong light on the retina of dogs, and by means of a plethysmograph and through measurements of the difference in the oxygen content of blood entering and leaving the brain, secured evidence of a dilatation of cerebral vessels when the optic nerve was stimulated. Cobb and his associates [3] stimulated the olfactory nerve of rabbits, and on histologic examination of the olfactory bulb found an unusually large number of open capillaries as compared with control sections. Other ingenious methods and important observations might be named.

Observations in man have necessarily been more inferential. We have observed that the flow of blood through the brain (as judged by measurement of the oxygen content of blood entering and leaving the brain) can be altered by variations in the oxygen and carbon

* Submitted for publication, May 13, 1931.

* From the Department of Neuropathology, Harvard Medical School, and the Thorndike Memorial Laboratory of the Boston City Hospital.

1. Forbes, H. S., and Wolff, H. G.: The Cerebral Circulation: III. The Vasomotor Control of Cerebral Vessels, Arch. Neurol. & Psychiat. **19**:1057 (June) 1928. Wolff, H. G., and Lennox, W. G.: The Cerebral Circulation: XII. The Effect on Pial Vessels of Variations in the Oxygen and Carbon Dioxide Content of the Blood, Arch. Neurol. & Psychiat. **23**:1097 (June) 1930.

2. Alexander, F. G.: Untersuchungen über den Blutgaswechsel des Gehirns, Biochem. Ztschr. **44**:127, 1912.

3. Cobb, S., and Talbott, J. H.: Studies in Cerebral Circulation: II. A Quantitative Study of Cerebral Capillaries, Tr. A. Am. Physicians **42**:255, 1927.

dioxide content of the blood and that such alterations may be the reverse of those taking place in an extremity.[4] Weiss and Lennox[5] demonstrated that the intravenous injection of histamine increased the flow of blood through vessels both inside and outside the skull, as well as through vessels of an extremity.

It is a common observation that flushing of the face and a feeling of warmth may accompany serious mental effort. By means of a thermocouple, Lombard[6] measured the temperature of the scalp in subjects who were roused to emotional or mental activity. The observed increases in the temperature of the skin were interpreted as heat from the working brain transmitted through the skull. Presumably the heat was due simply to the dilatation of cutaneous vessels. Though not proved, it seems logical that vessels inside and outside the head should respond to a given stimulus in the same manner if not to the same degree. The most convincing evidence of alteration in the flow of blood with reference to cerebral activity is the case of Fulton.[7] His patient had an arteriovenous aneurysm in the optic area of the meninges overlying the occipital lobe; this was revealed at an operation by Cushing. A bruit which was audible through the occipital bone became accentuated when the patient read, being loudest when reading was done in a dim light.

METHODS

We have approached the problem through the measurement of the gases in the blood drawn from the internal jugular vein of persons before, during and after the performance of mental work. Such observations have been made at intervals during the past three years and have already been reported in abstract.[8]

The subjects used were patients with epilepsy who were being treated in the Neurological Service of the Boston City Hospital. They were required to lie quietly with the eyes covered for at least half an hour before blood was withdrawn from the internal jugular vein. After the preliminary sample of blood was taken, a paper containing short problems in arithmetic was held before the subject's eyes; these problems he was asked to read and solve. After approximately five minutes, while the subject continued his efforts, blood was again withdrawn. In some

4. Lennox, W. G.: The Effect on the Intracranial and Peripheral Blood Flow in Man of Changes in the Blood Gases, to be published.

5. Weiss, S., and Lennox, W. G.: The Effect of Histamine on Intracranial and Peripheral Circulation, to be published.

6. Lombard, J. S.: Experimental Researchs on the Regional Temperature of the Head, London, H. K. Lewis & Company, 1879.

7. Fulton, J. F.: Observations upon the Vascularity of the Human Occipital Lobe During Visual Activity, Brain **51**:310, 1928.

8. Lennox, W. G.: Observations of the Intracranial Circulation in the Human Subject, Proc. Am. Soc. Clin. Investigation, 1929; J. Clin. Investigation **7**:517, 1929.

instances a third sample was taken after a rest period of from ten to fifteen minutes. Blood was taken without exposure to air, and analysis was begun at once in the apparatus of Van Slyke[9] and by the method described by Van Slyke and Neill.[10] The method of securing blood from the internal jugular vein was essentially that described by Myerson, Halloran and Hirsch.[11]

RESULTS

It will be recognized that certain difficulties might easily obscure the results to be obtained. It is difficult for the subject either to "make his mind a blank" or to concentrate on the problems set before him

Gaseous Content of Blood from the Internal Jugular Vein with Reference to Performance of Mental Work

	Before			During			After		
	Oxygen		Carbon Dioxide	Oxygen		Carbon Dioxide	Oxygen		Carbon Dioxide
Subject	Content	Capacity	Content	Content	Capacity	Content	Content	Capacity	Content
Bur	7.9	13.9	55.5	7.4	13.9	55.8	7.0	13.9	55.4
Fel	12.7	19.1	52.4	15.2	19.9	49.5	12.9	21.6	51.4
De G	14.5	22.6	55.8	15.7	22.7	54.7	14.7	22.1	55.5
Cla	4.9	12.0	60.2	7.8	12.0	57.4	6.8	12.1	57.8
Pen	10.9	18.7	54.0	11.7	18.7	53.5	10.2	18.7	53.6
McD	12.8	20.5	57.4	13.5	20.5	57.1	12.0	20.5	57.3
Average	10.6	17.8	55.9	11.9	17.9	54.7	10.6	18.1	55.2
Fie	13.1	21.5	52.4	12.6	20.0	53.0			
Wad	11.6	17.5	48.6	10.6	17.3	49.5			
McL	14.3	19.1	55.7	13.9	19.0	55.9			
Dev	10.9	19.3	57.8	10.7	19.5	56.5			
Hen	11.0	19.0	56.3	11.1	19.0	56.0			
Dev.[2]	12.6	18.8	55.0	13.7	18.8	53.9			
Edw	11.0	17.7	53.7	13.7	17.7	52.1			
Pow	15.4	24.7	54.2	17.7	25.1	52.6			
Col	13.4	21.8	55.5	15.1	21.7	53.1			
Average of all	11.8	19.0	54.9	12.7	19.0	54.0			
Control									
Brl	12.7	20.0	59.8	12.7	....	59.7			
Brl.[2]	12.7	20.0	59.8	12.8	....	59.4			
Sta	8.2	15.1	54.2	8.4	....	54.0			
Mit	11.1	17.6	56.2	10.9	....	56.2			
Average	11.2	18.1	57.5	11.2	....	57.3			

while a needle is being inserted deeply into his neck. The degree of apprehension or of discomfort may not have been the same each time that blood was withdrawn. To meet this objection, in the later obser-

9. Van Slyke, D. D.: Portable Form of Manometric Gas Apparatus and Certain Points in Technique of Its Use, J. Biol. Chem. **73**:121, 1927.

10. Van Slyke, D. D., and Neill, J. M.: The Determination of Gases in the Blood and Other Solutions by Vacuum Extraction and Manometric Measurements, J. Biol. Chem. **51**:523, 1924.

11. Myerson, A.; Halloran, R. D., and Hirsch, H. L.: Technique for Obtaining Blood from the Internal Jugular and Internal Carotid Artery, Arch. Neurol. & Psychiat. **17**:807, 1927.

vations we withdrew blood at intervals from a needle left in situ. Results by this method were much the same as with the method of separate punctures.

Another important question is that of control observations. On a number of occasions blood was taken at ten or fifteen minute intervals, the subject lying quietly throughout the procedure. Although some variation was present in such successively drawn samples of blood from the jugular vein, alteration was not as great as in specimens taken from a vein of the arm or leg. The average of a dozen jugular measurements showed no significant difference in the gaseous content

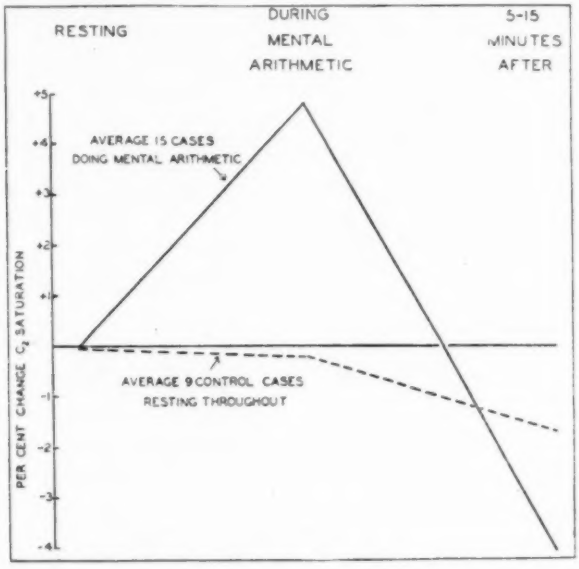

Chart showing average change in oxygen saturation of the blood before, during and after mental work. Compare with the table.

of blood drawn at short intervals. Four examples are given in the accompanying table.

Fifteen observations on the effect of mental work were made. In five instances the oxygen content of blood from the internal jugular vein was less during this period than before (the average decrease being 0.5 per cent by volume). In ten, it was increased (the average increase being 1.6 per cent by volume). In the whole group of fifteen observations, the average oxygen content of the blood was increased during mental work by 0.9 per cent by volume, with a corresponding decrease in the carbon dioxide content.

In six of the experiments a third sample of blood was taken after the subject had been allowed to rest with eyes covered for from ten

to fifteen minutes. During the performance of mental arithmetic the average oxygen content of the blood was increased by 1.3 per cent by volume and the carbon dioxide content decreased by 1.2 per cent by volume. The oxygen content of the third sample was the same as that of the specimen taken at the preliminary puncture (see chart).

These changes are not of the magnitude observed when there is an alteration of the carbon dioxide content of the arterial blood. We believe, however, that they are significant and not accidental variations. Though the differences in the oxygen content of blood are not absolutely large, they are distinctly greater than changes observed in the control series. The observations indicate that in the majority of persons mental effort results in blood leaving the brain in a slightly more arterial-like condition. This cannot be due to a decreased use of oxygen, for we must suppose that increased cerebral activity is associated with an increased consumption of oxygen. The result can be explained by a dilatation of cerebral vessels with a resulting increase in the speed of blood flow through the brain, a factor that outweighs the increased consumption of oxygen. Such an explanation is consistent with the observations in the literature that have been mentioned. We do not know the mechanism by which this dilatation takes place (whether nervous or chemical in origin), nor did we ascertain whether there were measurable differences in the flow of blood in other portions of the body.

It is to be expected that increased activity of nervous as well as of muscular tissues should call for a larger supply of blood containing a higher oxygen content. Hrdlicka, the noted anthropologist, says that man's intellectual powers have not reached their full possibilities because the development of the cerebral circulation has not kept pace with the development of the brain. We know that anoxemia results in loss of consciousness, but apparently the effect on mental acuity of an excess supply of oxygen to the brain has not been investigated.

An interesting question is whether mental effectiveness is related to the readiness with which the cerebral circulation responds to mental effort. Our subjects were of varying degrees of intelligence; some were university students or graduates and some showed slight mental deterioration. We were not able, perhaps because of the smallness of the group, as well as of the lack of mental contrast in its members, to relate the successful performance of the task imposed to the degree of the circulatory response. We know that the circulatory apparatus of the trained athlete shows a comparatively small response to physical work. It is possible that a greater response of the cerebral circulation would be present in persons who performed the tasks imposed less readily than our subjects performed them. The problem is not clearcut

because (in an effort to secure a maximum response) the task given the subjects called sensory (optic) nerve centers as well as intellectual processes into play. Subject Pen. was blind and "read" the problems with his finger tips. He was one of the ten whose blood gave evidence of a dilatation of cerebral vessels.

In eleven of the experiments we measured the gaseous content of the arterial blood. The average calculated respiratory quotient (the increase in the carbon dioxide content of venous blood divided by the decrease in its oxygen content) was the same (0.86) in the work as in the rest period.

SUMMARY

In fifteen instances, blood from an internal jugular vein was taken before and during the reading and performance of problems in mental arithmetic. In two thirds of the instances there was an increase in the oxygen content and a decrease in the carbon dioxide content of the blood leaving the brain. The average increase in oxygen content for the fifteen cases was 0.9 per cent by volume, an amount well outside the limits of average normal variation. The observed increases are presumably due to a dilatation of cerebral vessels.

THE CEREBRAL CIRCULATION

XVI. CHANGES IN THE HUMAN RETINAL CIRCULATION AND IN THE PRESSURE OF THE CEREBROSPINAL FLUID DURING INHALATION OF A MIXTURE OF CARBON DIOXIDE AND OXYGEN *

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In the twelfth paper of this series, Wolff and Lennox [1] showed by experiments on animals that an increased concentration of carbon dioxide increases the volume of blood passing through the brain by raising the systemic blood pressure and by dilating the cerebral arteries. Venous blood becomes more arterial-like (richer in oxygen and poorer in carbon dioxide). They expressed the belief that the most effective measure for increasing the supply of blood, and hence of oxygen, to the tissues of the brain is the inhalation of a mixture of 90 per cent oxygen and 10 per cent carbon dioxide. The latter increases the diameter of arteries and, by inducing a condition of acidosis, increases the dissociation of oxygen from hemoglobin and makes more oxygen available for the tissues. It also stimulates respiration and increases the blood pressure.

It is, of course, impracticable to duplicate such experiments on human beings, but we have been able to make certain observations on patients that appear to corroborate the experimental observations of Wolff and Lennox. Since the discovery of Loevenhart and his co-workers [2] that breathing mixtures rich in carbon dioxide and oxygen could arouse patients from stupor, there has been much interest and speculation as to the physiologic mechanism of this psychologic change. In this clinic the treatment was tried on several patients in states of mental or physical retardation. In five cases of chronic encephalitis with rigidity, bradykinesia and other "parkinsonian" symptoms, the patients reported immediate improvement and wished to repeat the treatment.

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* Submitted for publication, May 13, 1931.

* From the Neurological Unit, Boston City Hospital and Department of Neuropathology, Harvard Medical School.

1. Wolff, Harold G., and Lennox, William G.: Cerebral Circulation: XII. The Effect on Pial Vessels of Variations in the Oxygen and Carbon Dioxide Content of the Blood, Arch. Neurol. & Psychiat. **23**:1097 (June) 1930.

2. Loevenhart, A. S.; Lorenz, W. F., and Waters, R. M.: Cerebral Circulation, J. A. M. A. **92**:880 (March 16) 1929.

Objective observation, however, has not justified such optimism; the patients did seem to be able to move somewhat more quickly while flushed with oxygen. One patient in partial extensor rigidity relaxed conspicuously for a few minutes, but the changes were transitory. In all these patients ophthalmoscopic observations were made of the eye-grounds while the inhalation was in progress, and a dramatic change was observed in the vessels of the fundus as the patient inhaled more and more of the mixture of oxygen and carbon dioxide; the veins, at first normally purple, began to appear red in one and one-half minutes, reaching a bright red almost as brilliant as that of the arteries in about six minutes. When the respirator was removed, the color of the veins returned to purple in from one and one-half to three minutes.

In case 2, the patient was observed with a Gullstrand ophthalmoscope. A color scale was made for comparison with the expected changes of color in the retinal vessels. Six shades of red were arranged in a series from arterial red (no. 1) to venous purple (no. 6), these two extremes being matched with the usual color of the artery and vein in the eye-ground of the patient before the inhalation began. The other hues (nos. 2, 3, 4 and 5) were made by adding increments of blue to the no. 1 red. In this way an arbitrary scale was prepared. This scale was kept beside the observer who was watching the retinal vessels, and every half minute he looked at the scale, compared with it the colors of the vessels and reported to a recorder the value of the colors in terms of the scale.

For general standardization, this scale may be compared to the colors in Ridgway's manual.[3] Arterial red no. 1, as seen in the eye-ground with the ophthalmoscope, corresponds closely with "coral red" (plate XIII); no. 2 is "jasper red" (plate XIII); no. 3 is between "jasper red" and "eugenia red," and no. 4 is "eugenia red." The venous purple, no. 6, is almost perfectly matched by "rose red" (plate XII), while no. 5 is between nos. 4 and 6. With these standards, a fairly accurate idea can be obtained of the changes occurring during the inhalation of carbon dioxide and oxygen, the time relations of which are given in the two protocols (tables 1 and 2).

At six minutes in protocol 1 (table 1) and six and one-half minutes in protocol 2 (table 2), the inhalation was stopped; in each case the vein had become so red that it was difficult to distinguish it from the artery. At four minutes in the first experiments and at five minutes in the second, the patient began to show hyperpnea; in each case this was the time when the vein first reached its maximum redness. Attempts were made to measure the diameters of the artery and vein, but they

3. Ridgway: Color Standards and Color Nomenclature, Washington, D. C., 1912.

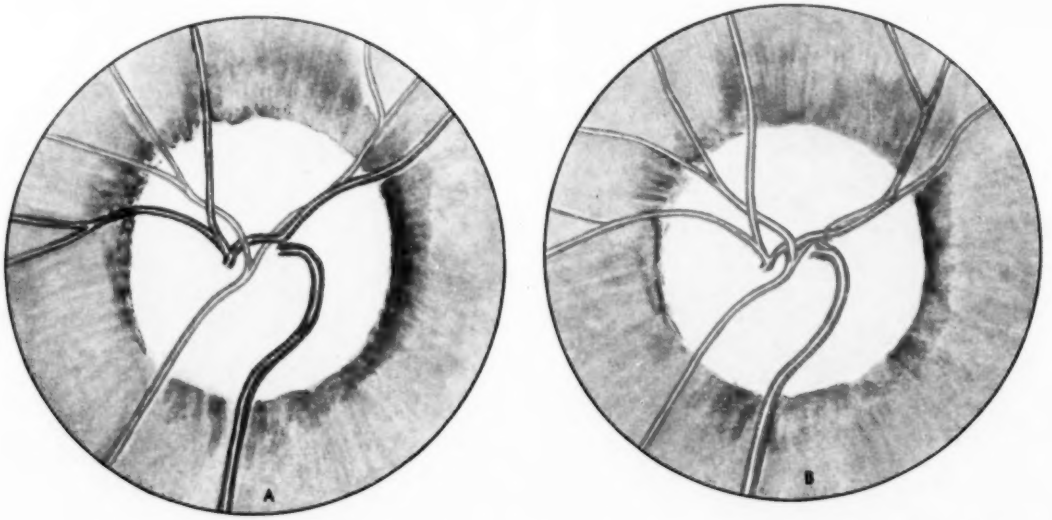

Fig. 1.—*A* shows the fundus of the left eye in case 2 as it ordinarily appeared and as it looked just before beginning the inhalation. Note that the arteries appear as a bright orange red and the veins a deep rose. *B* shows the condition after six and one-half minutes' inhalation of a mixture of carbon dioxide and oxygen; the arteries and veins are almost indistinguishable by their color. These water color sketches were made by one of us (S. C.) immediately after the observations, by using notes made at the time of the experiment.

were not successful. It was observed that the ratio between the caliber of the larger arteries and veins changed; at first, this ratio was approximately $\frac{v}{a} = \frac{4}{6}$, changing at the time of hyperpnea to $\frac{v}{a} = \frac{4}{5}$, i. e., the diameter of the vein approached that of the artery.

Comparison of these observations with experiment 92 of Wolff and Lennox [1] (their fig. 16) shows that they, too, found that changes in

TABLE 1.—*Protocol of Case 2, Observation 1, September, 1929*

Time	Color of Artery	Color of Vein	Comment
11 : 40	1	6	Control observation
11 : 52½	1	6	Started inhalation of 10% CO_2 and 90% O_2
1 min. after	2	6	
1½ min. after	2	4	
2 min. after	2	3	
2½ min. after	2	3	
3 min. after	2	3	
3½ min. after	1	3	
4 min. after	1	2-3	Marked hyperpnea
4½ min. after	1	2	Marked hyperpnea
5 min. after	1	2	
5½ min. after	1	2	
6 min. after	2	4	Stopped inhalation
½ min. after stopping	2	5	
1 min. after stopping	2	5	
1½ min. after stopping	1-2	6	
2 min. after stopping	2	6	

TABLE 2.—*Protocol of Case 2, Observation 2*

Time	Color of Artery	Color of Vein	Comment
	1	6	Control observation
	1	6	Started inhalation of 10% CO_2 and 90% O_2
½ min. after	1	6	
1 min. after	2	6	
1½ min. after	2	6	
2 min. after	2	4	
2½ min. after	1	4	
3 min. after	1	3	
3½ min. after	1	3	
4 min. after	1	3	
4½ min. after	1	3	
5 min. after	1	2-3	Marked hyperpnea
5½ min. after	1	2-3	
6 min. after	1	2-3	
6½ min. after	..	..	Stopped inhalation
1 min. after stopping	1	4	
2 min. after stopping	1	4	
3 min. after stopping	2	6	

respiration occurred before the maximal changes in the blood vessels. For example, experiment 77, which was carried out like our treatments, with 10 per cent carbon dioxide and 90 per cent oxygen, is illustrated by their figure 6. In these experiments, and in others by Forbes,[4] changes in color occurred in the pial vessels similar to those seen in the retinal vessels of our patients. We did not observe definite changes in the caliber of the arteries and veins of the retina, but one could

4. Forbes, H. S.: Personal communication.

hardly expect to recognize these without a micrometer scale on the ophthalmoscope, and though we tried this it did not give satisfactory results because of poor illumination and the impossibility of keeping the patient still.

Observations of the changes in the pressure of the cerebrospinal fluid were made in case 1 during inhalation of carbon dioxide (10 per cent) and oxygen (90 per cent). These are charted in figure 2; it is obvious that both in the cat (Wolff and Lennox) and in the man a marked rise in intracranial pressure occurs during inhalation of this gaseous mixture. In addition, it is interesting to note that voluntary hyperpnea in man has been frequently observed by one of us (F. F.-S.) to lower the pressure of the cerebrospinal fluid (fig. 3). Similarly, artificial hyperpnea in

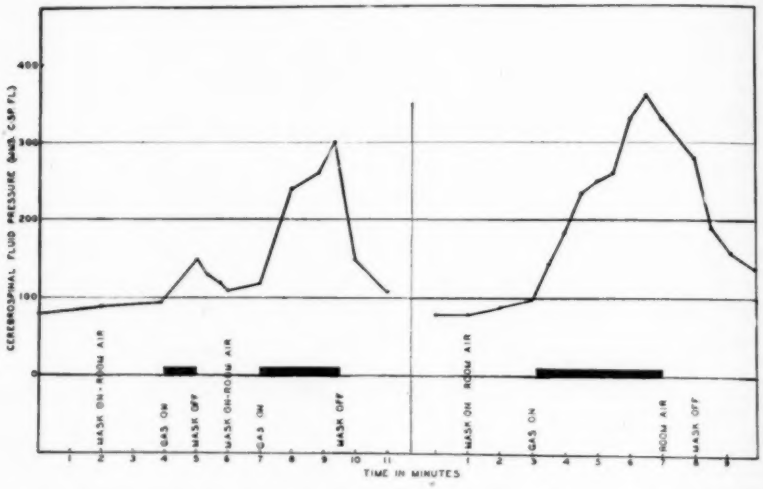

Fig. 2.—The rise in pressure of the spinal fluid produced by the inhalation of a mixture of 10 per cent carbon dioxide and 90 per cent oxygen is shown. It will be noted that in each instance the rise in the pressure of the spinal fluid occurred as soon as the mixture was breathed, and the pressure fell as soon as the patient began to breathe room air again. Such a rapid increase in pressure could not be due to increased formation of cerebrospinal fluid. This is further borne out by the rapid return to normal pressure. We attribute the increase in pressure to a cerebral vascular dilation. The findings are quite analogous to those observed in cats by Wolff and Lennox (ARCH. NEUROL. & PSYCHIAT. **23**:1097 [June] 1930).

animals (Wolff and Lennox,[1] fig. 3) lowers the pressure of the spinal fluid, as well as causing constriction of the pial arteries. Taking all these data into consideration, it seems reasonable to interpret the increase in the pressure of the cerebrospinal fluid during inhalation of a mixture of carbon dioxide and oxygen as due to cerebral vascular dilatation.

There seem to be two possible explanations of the change in color in the vessels: 1. The inhalation of the carbon dioxide and oxygen might so saturate the tissues with oxygen that in passing through the capillary bed the blood loses almost no oxygen. Arterial blood, however, is always 95 per cent saturated so that a slight percentage of increase could hardly cause this marked change in color. 2. The arterioles of the retina might open widely and allow the blood to flow so rapidly through the capillary bed that it loses no appreciable amount of oxygen, thus retaining its red color.

In the light of the work of Forbes,[5] who first photographed in color the living cerebral vessels, and the already quoted observations of Wolff and Lennox, the latter explanation seems by far the more logical.

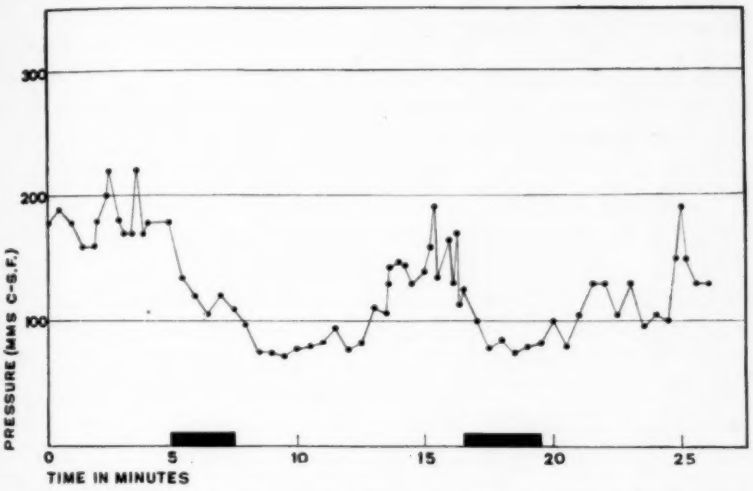

Fig. 3.—The effect of voluntary hyperpnea on the pressure of the cerebrospinal fluid is shown. In contrast to the influence of hyperpnea produced by carbon dioxide, the overbreathing of room air (indicated by black blocks) causes a prompt fall in the pressure of the cerebrospinal fluid. The return to normal is considerably slower than when carbon dioxide is inhaled. The fall in pressure is frequently much more marked than is shown here, the pressure occasionally falling to zero after twenty or thirty deep breaths. We attribute the fall in pressure partly to the withdrawing of blood from the cerebral veins as the result of the increased negative intrathoracic pressure, and perhaps partly to a cerebral vasoconstriction that was observed in similar experiments in cats by Wolff and Lennox (ARCH. NEUROL. & PSYCHIAT. **23**:1097 [June] 1930).

It may be supposed, then, that the symptomatic changes (the coming out of stupor and the decrease in rigidity and bradykinesia observed in such patients) were due in part to cerebral vascular dilatation which

5. Forbes, H. S.: The Cerebral Circulation: I. Observation and Measurement of the Pial Vessels, Arch. Neurol. & Psychiat. **19**:751 (May) 1928.

caused an increase in the supply of blood to the nerve cells. This involves an increased supply of oxygen and a freer washing out of metabolites. There may be, in addition, however, a narcotic effect from the carbon dioxide. If this is the case, the change in motility may be an expression of the direct action of the carbon dioxide on the nerve cell.[6] Cases are known in which the intravenous administration of sodium iso-amylethyl barbiturate had the same effect on catatonic stupor as the administration of mixtures of carbon dioxide and oxygen.[7] Nevertheless, it is conceivable that the increased supply of oxygen to the nerve cells may be a factor in the sometimes dramatic symptomatic improvement. (Per contra, one might speculate as to the possibility that in chronic encephalitis the symptoms of parkinsonism were caused by chronic hypo-oxemia of the nerve cells, causing first functional deficiency and finally necrobiosis.)

6. Wolff, H. G.: Personal communication, 1931.

7. Bleckwenn, W. J.: Narcosis as Therapy in Neuropsychiatric Conditions, J. A. M. A. **95**:1168 (Oct. 18) 1930.

THE CEREBRAL CIRCULATION

XVII. CEREBRAL BLOOD FLOW AND THE VASOMOTOR RESPONSE OF THE MINUTE VESSELS OF THE HUMAN BRAIN TO HISTAMINE *

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In previous communications,[1] Weiss, Lennox, Robb and Ellis have presented evidence which indicates that the minute cerebral blood vessels of man respond with dilatation to histamine. A quantitative comparison reveals a marked sensitivity of the cerebral blood vessels to this substance. Histamine base administered intravenously in doses of from 0.001 to 0.003 mg. produces a dilatation of the arterioles. So small an amount of histamine may be present in the circulating blood under physiologic or pathologic conditions.

The evidence presented previously regarding the dilatation of the cerebral vessels in man was based on: (1) Simultaneous studies of the arterial and venous blood pressures, the cerebrospinal fluid pressure and the degree of the pulsatile expansion of this fluid. These observations revealed that histamine causes a marked increase in the pulsatile expansion and the pressure of the cerebrospinal fluid, without change in the arterial or venous blood pressures. Such a change indicates dilatation of the arterioles of the cerebral blood vessels. (2) Observations of the surgically exposed surface of the human brain. These studies revealed a flush, an expansion and an increased pulsation of this area. (3) Quantitative graphic registration of the expansive movements of the brain and the cerebrospinal fluid, together with measurements of the arterial and venous blood pressures, in a patient with a postoperative cranial defect. These observations also indicated an increased pulsation of the brain due to histamine. The three types of observations supported each other.

* Submitted for publication, June 4, 1931.

* From the Departments of Neuropathology and Medicine of the Harvard Medical School and the Thorndike Memorial Laboratory of the Boston City Hospital.

1. Weiss, S.; Lennox, W. G., and Robb, G. P.: The Dilator Effect of Histamine on the Cerebral Vessels in Man, Proc. Soc. Exper. Biol. & Med. **26**:706, 1929. Weiss, S.; Ellis, L. B., and Robb, G. P.: Bodily Responses in Man During the Continuous Intravenous Administration of Histamine, Am. J. Physiol. **90**:551, 1929; The Systemic Effects of Histamine in Man with Special Reference to the Responses of the Cardiovascular System, Arch. Int. Med., to be published.

The present communication is concerned mainly with the effect of histamine on the cerebral blood flow in man. Because a correlation exists between dilatation of the arterioles and an increase in blood flow, the latter may serve as a measure of the changes in the cross-sectional area of the arterioles.

METHODS OF STUDY

The subjects used in this investigation were eight young male adults suffering from epilepsy who were accustomed to venous punctures. They were in a basal state and lay quietly in a horizontal position for at least half an hour before the first specimen of blood was drawn. In order to reduce the pain to a minimum, local anesthesia of the skin was induced with procaine hydrochloride. Blood was taken from the internal jugular vein by the method of Myerson, Halloran and Hirsch.[2] In addition, blood was taken from the external jugular and basilic veins and from the cubital or radial artery. The blood was obtained under oil without stasis, and the analysis was begun at once. Control blood samples were taken before the continuous infusion of histamine was started, using an arrangement previously described.[3] Following the continuous intravenous infusion of a histamine phosphate solution of 1:10,000 concentration, at a rate that varied between 0.5 and 1 cc. per minute, samples were obtained from the same blood vessels. A portable, constant volume, blood-gas apparatus and the method of Van Slyke[4] were used. In each blood sample the oxygen content and capacity and the carbon dioxide content were measured in duplicate.

The arterial and venous blood pressures were taken before and repeatedly during the injection of histamine. The arterial blood pressure was measured by both the auscultatory and the Tycos graphic methods. The venous pressure was determined by the direct method of Moritz and Tabora.[5]

In five of the eight subjects, the cardiac output before and during the administration of histamine was measured by the method of Bock, Gildea and Lathrop,[6] and changes in the surface temperature were determined by a calibrated thermocouple.[7] The cardiac output and skin temperature were again measured under similar conditions from one to three days after the blood-gas studies were made. Although the total amount of histamine administered varied, the rate of infusion was the same as in the experiments in which the blood gases were studied.

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2. Myerson, A.; Halloran, R. D., and Hirsch, H. L.: Technic for Obtaining Blood from the Internal Jugular Vein and Internal Carotid Artery, Arch. Neurol. & Psychiat. **17**:807 (June) 1927.

3. Weiss, Robb and Ellis (footnote 1, third reference).

4. Van Slyke, D. D.: Note on a Portable Form of Manometric Gas Apparatus and on Certain Points in Technique of Its Use, J. Biol. Chem. **73**:121, 1927.

5. Moritz, F., and Tabora, D. V.: Ueber eine Methode beim Menschen den Druck im oberflächlichen Venen exact zu bestimmen, Deutsches Arch. f. klin. Med. **98**:475, 1910.

6. Field, H., Jr.; Bock, A. V.; Gildea, E. F., and Lathrop, F. L.: The Rate of the Circulation of the Blood in Normal Resting Individuals, J. Clin. Investigation **1**:65, 1924.

7. Benedict, F. G.: Die Temperatur der menschlichen Haut, Ergebn. d. Physiol. **24**:594, 1925.

RESULTS

The gaseous contents of the various blood samples obtained are shown in table 1. The measurements for the blood obtained prior to

TABLE 1.—*The Gaseous Content of Blood from Various Vessels Before and During the Injection of Histamine*

Case	Age	Duration of Histamine Infusion, Min.	Histamine Phosphate, Mg.	Oxygen Content		Oxygen Capacity		Carbon Dioxide Content	
				Before	During	Before	During	Before	During
Artery									
1	19	60	5.0	....	....	....	....	....	....
2	32	55	4.5	....	....	....	....	....	....
3	24	56	2.9	23.8	27.6	25.2	28.3	46.8	44.3
		60	4.0	19.9	21.9	21.0	22.7	49.5	47.3
4	20	60	5.0	22.4	24.3	23.1	25.0	51.3	48.9
5	24	40	2.9	22.1	23.5	23.0	23.9	48.3	45.0
6	27	48	3.0	19.1	20.3	20.2	21.9	46.4	45.2
7	23	57	4.0	22.4	22.5	24.1	24.2	48.0	47.7
8	28	31	3.0	17.3	17.9	18.0	19.6	50.5	50.3
Average				21.0	22.6	22.1	23.7	48.7	46.4
Internal Jugular Vein									
1	19	60	5.0	14.3	16.5	22.1	23.3	58.1	53.4
2	32	55	4.5	13.2	15.8	16.1	16.9	57.1	53.3
3	24	56	2.9	18.4	19.3	23.0	24.1	51.7	49.8
		60	4.0	12.3	14.2	20.8	22.1	57.5	54.1
4	20	60	5.0	16.1	22.9	21.9	23.5	58.0	49.4
5	24	40	2.9	15.7	22.8	22.7	23.7	56.1	46.8
6	27	48	3.0	14.6	15.9	17.2	20.8	54.8	51.8
7	23	57	4.0	16.3	17.0	22.3	22.6	54.8	53.5
8	28	31	3.0	11.9	12.0	20.4	19.6	56.0	56.3
Average				14.8	17.4	20.7	21.8	56.0	52.0
External Jugular Vein									
1	19	60	5.0	21.0	24.2	24.7	25.1	51.4	44.0
2	32	55	4.5	15.2	15.7	16.2	16.7	51.3	50.5
3	24	56	2.9	22.4	27.8	25.0	28.1	47.5	44.3
		60	4.0	20.3	21.1	21.3	22.4	49.2	48.0
4	20	60	5.0	21.4	24.0	22.8	24.5	53.4	49.2
5	24	40	2.9	21.4	23.2	22.8	23.8	50.8	45.3
6	27	48	3.0	18.9	19.8	19.4	21.7	48.4	47.3
7	23	57	4.0	21.6	23.9	23.5	24.1	51.9	47.0
8	28	31	3.0	16.1	17.4	19.1	19.6	51.7	49.6
Average				19.8	21.9	21.6	22.9	50.6	47.3
Antecubital Vein									
1	19	60	5.0	14.4	17.8	20.4	20.9	57.2	47.9
2	32	55	4.5	11.0	13.2	16.7	18.9	55.1	50.8
3	24	56	2.9	18.8	25.0	23.4	25.4	50.7	47.8
		60	4.0	13.7	17.4	20.6	22.3	54.0	49.2
4	20	60	5.0	16.8	21.8	21.5	22.5	57.1	52.1
5	24	40	2.9	17.9	21.1	22.3	23.5	54.2	48.9
6	27	48	3.0	15.6	17.1	17.1	18.2	54.1	51.6
7	23	57	4.0	18.9	19.6	22.7	22.8	53.3	50.2
8	28	31	3.0	8.2	13.6	18.9	19.6	57.0	53.2
Average				13.9	18.5	20.4	21.6	54.7	50.2

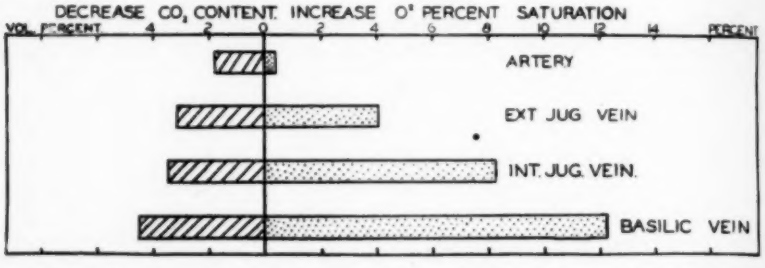
the injection of histamine are similar to those reported by Lennox [8] for a larger series of subjects except that, in the present group, blood from the internal jugular vein contained slightly more oxygen.

8. Lennox, W. G.: The Oxygen and Carbon Dioxide Content of Blood from the Internal Jugular and Other Veins, Arch. Int. Med. **46**:630 (Oct.) 1930.

During the injection of histamine, there was always an increase in the oxygen content of the blood from the different veins, with the exception of patient H., whose blood from the internal jugular vein contained 0.3 per cent by volume more carbon dioxide during than before the administration of histamine. The amount of the difference

TABLE 2.—*Average Changes in the Gaseous Content of Blood Taken from Various Vessels Before and During the Injection of Histamine*

	Artery		Internal Jugular Vein		External Jugular Vein		Antecubital Vein	
	Oxygen Percentage of Saturation	Carbon Dioxide Content	Oxygen Percentage of Saturation	Carbon Dioxide Content	Oxygen Percentage of Saturation	Carbon Dioxide Content	Oxygen Percentage of Saturation	Carbon Dioxide Content
Before.....	95.0	48.7	71.3	56.0	91.6	50.6	73.7	54.7
During.....	95.4	46.9	79.6	52.4	95.7	47.3	85.9	50.2
Change....	+0.4	—1.8	+8.3	—3.6	+4.1	—3.3	+12.2	—4.5



The average change in the oxygen and carbon dioxide content of the blood in the artery and veins during the injection of histamine.

in the blood contents during the period of control and after the injection of histamine varied in the different patients. Since, according to control observation, the gaseous content of blood from the peripheral veins of the same individual may vary at different times while the patient is lying at rest, we lay more stress on the average results obtained than on any individual measurement. These average results are shown in table 2 and the accompanying chart. As a measure of the oxygen content of the blood, the percentage of saturation was calculated. This percentage rather than the actual figure for the oxygen content was used because it was found that the oxygen capacity of the blood before and during the injection regularly showed a variation. The oxygen saturation of the bloods during histamine injection, in relation to their saturation before, showed the following average increases: in the artery, 0.4 per cent by volume; in the external jugular vein, 4.1 per cent by volume; in the internal jugular vein, 8.3 per cent by volume, and in the antecubital vein, 12.2 per cent by volume.

The systemic response of the subjects during the administration of histamine was similar to that observed previously.[3] The systolic arterial blood pressure showed no essential changes; the diastolic pressure remained unaltered or became moderately lower. The venous pressure remained unaltered or became slightly elevated during the administration of histamine, as indicated in table 3. The cardiac output was increased in three and essentially unaltered in two cases. There was no relationship between changes in the cardiac output and the cerebral blood flow. The basal metabolism was distinctly elevated in three cases during the

TABLE 3.—*The Effect of Histamine on the Cardiac Rate, Arterial and Venous Blood Pressure, Cardiac Output, Respiration and Metabolism*

Case	Cardiac Rate, per Min.	Arterial Blood Pressure		Venous Pressure, Mm. of Water	Carbon Dioxide Tension			Carbon Dioxide Output per Minute, Cc.	Respiratory, Minute Volume, L.	Cardiac Output per Minute, L.	Cardiac Output per Beat, Cc.	Respiratory Quotient	Basal Metabolic Rate, per Cent	Histamine Phosphate Received, Mg.	Before or During Histamine
		Systolic, Mm. of Mercury	Diastolic, Mm. of Mercury		Alveolar, Mm. of Mercury	Virtual Venous, Mm. of Mercury	Difference, Mm. of Mercury								
1	65	114	76	75	34.6	45.8	11.2	197	6.2	3.9	59	0.777	+ 7	...	Before
	108	125	70	100	37.5	46.4	8.9	216	6.9	5.4	50	0.750	+22	4.9	During
2	72	108	70	30	40.3	44.9	4.6	147	4.8	7.8	108	0.744	± 0	...	Before
	93	110	60	50	39.3	45.8	6.5	203	6.0	7.4	79	0.683	+30	5.0	During
3	83	136	84	110	43.8	51.5	7.7	222	5.8	7.0	84	0.742	+28	...	Before
	120	125	65	140	44.3	51.0	6.7	229	6.2	8.5	70	0.737	+33	4.0	During
6	85	110	70	60	41.0	53.6	12.5	327	9.5	6.2	73	0.995	+45	...	Before
	87	116	72	70	41.2	50.9	9.7	279	8.7	6.9	79	0.953	+34	4.1	During
7	72	104	68	55	42.4	49.1	6.7	216	7.0	7.9	109	0.875	+ 4	...	Before
	100	102	64	85	42.5	48.4	5.9	224	7.7	9.4	99	0.766	+23	4.0	During

administration of histamine; in the other two subjects it was essentially unaltered.

Measurements of the skin temperature, as described in a previous study, showed an elevation of the skin temperature especially over the upper (cephalic) part of the body in four cases during the administration of histamine. In the fifth there was no change, although a marked flush was present and the cutaneous venules were dilated. The significance of this type of cutaneous reaction has been discussed elsewhere.[3]

COMMENT

The moderate change observed in the oxygen saturation of the external jugular blood might be expected because of the fact that this blood was nearly arterial to begin with. In order to explain the marked increase in the oxygen saturation of the blood within the internal jugular and basilic veins, however, one must assume that there was either a decrease in the metabolic rate of the tissues through which the blood

passed or else an increased rate of blood flow. Previous observations made by Weiss, Robb and Ellis [3] and measurements of the respiration and metabolism during the administration of histamine in five of the subjects studied indicate that the metabolism is increased, not decreased. Thus, the observations on the oxygen content signify that during the administration of histamine the blood flow through the brain is increased. It has been shown previously as well as in the subjects observed in this study that during histamine injection the total blood volume as well as the mean velocity of blood flow is increased due to peripheral vasodilatation. It was postulated by Weiss, Robb and Ellis [3] that in man not all vascular areas respond with dilatation to histamine. The observations reported here, together with those described before, indicate that the cerebral arteriolar bed responds to histamine with dilatation. Probably the closed-box arrangement of the skull prevents the intracranial vessels from dilating to as great an extent as do the vessels of the arm. This assumption is supported by the fact that the minimal amount of histamine that produces arteriolar dilatation of the cerebral vessels is considerably less than the amount that is essential to induce relaxation of the cutaneous arterioles of the arms, as indicated by changes in the skin temperature and oxygen saturation of the blood from the cubital vein. Thus, although the degree of dilatation of the cerebral arterioles is less than that of the cutaneous arterioles of the arm, the sensitivity of the cerebral vessels is considerably greater. This study of the dilator effect of histamine on the cerebral vessels of man is corroborated by the observations of Forbes, Wolff and Cobb [9] on the pial vessels of the cat. Using a window screwed into the skull of a cat, they observed the dilatation of the pial vessels consequent to the systemic injection of histamine.

The constant decrease in the carbon dioxide content of the blood from the vascular areas studied may be due to one or a combination of three conditions: (1) a decrease in metabolism with no corresponding decrease in blood flow, (2) an overventilation of the lungs and (3) an increased blood flow. In view of the fact that the metabolism is increased and that overventilation of the lungs does not accompany the administration of histamine, the first two conditions can be ruled out. The question may be raised whether the decrease in carbon dioxide could have affected secondarily the peripheral vessels. Wolff and Lennox [10] observed the pial vessels of the cat while the animals breathed various mixtures of oxygen and carbon dioxide, and Lennox [11] under-

9. Forbes, H. S.; Wolff, H. G., and Cobb, S.: The Cerebral Circulation: X. The Action of Histamine, Am. J. Physiol. **89**:266, 1929.

10. Wolff, H. G., and Lennox, W. G.: The Cerebral Circulation: XII. The Effect on Pial Vessels of Variations in the Oxygen and Carbon Dioxide Content of the Blood, Arch. Neurol. & Psychiat. **23**:1097 (June) 1930.

11. Lennox, W. G.: Observations Concerning Cerebral Circulation in Man. Proc. Am. Soc. Clin. Investigation, May, 1930; J. Clin. Investigation **9**:16, 1930.

took similar experiments on man. Both these observations showed that an increased inhalation of oxygen and a decreased inhalation of carbon dioxide would cause a constriction rather than a dilatation of the intracranial vessels. Thus the dilatation observed cannot be attributed to changes in the carbon dioxide content of the blood. In our experiments the decrease in the carbon dioxide content of arterial blood (1.8 per cent by volume) was small, and therefore it is questionable whether this factor could have influenced the state of the cerebral vessels.

During the injection of the histamine there was an increase in the average oxygen capacity of the venous blood obtained from different veins. This varied from an increase of 1.1 per cent by volume for the internal jugular blood to 1.6 per cent by volume for the arterial blood. This increased concentration of oxygen in the blood can be explained: (1) by an increased output of red cells from the spleen or elsewhere into the circulation, or (2) by an increased passage of the fluid portion or the whole plasma through the walls of the peripheral vessels. It has been shown previously [3] that there is no appreciable increase in the number of red blood cells or in the young red or white blood cells. The increase in oxygen capacity can therefore be attributed to transudation of the blood plasma through the altered capillaries.[3] This is in harmony with the observation of Dale and Laidlow on animals.[12] In the arterial blood, the increase in oxygen capacity was nearly matched by an increase in oxygen content, so that the percentage saturation remained the same.

In three instances, during the administration of histamine to patients with epilepsy, convulsive seizures occurred. We do not believe that histamine induced these attacks, but we attach considerable importance to the fact that even though the blood flow through the brain was increased, the development of the seizures was not prevented. This observation favors the concept that epileptic seizures do not invariably depend on ischemia and oxygen deficiency.

Weiss and Ellis,[13] in studying the effect of lesions of the higher vasomotor centers in patients with hemiplegia, called attention to the fact that a number of nervous, chemical and mechanical responses of the minute vessels of various parts of the body indicate that the vasomotor response and sensitivity of the minute vessels is greater in the upper than in the lower portion of the body. It has been suggested that the progressive increase of resistance of the minute vessels from the head toward the feet is of special teleologic and physiologic signifi-

12. Dale, H. H., and Laidlow, P. P.: Histamine Shock, J. Physiol. **52**:355, 1919.

13. Weiss, S., and Ellis, L. B.: The Circulatory Mechanism and Unilateral Edema in Cerebral Hemiplegia, J. Clin. Investigation **9**:17, 1930.

cance in man, whose body is disproportionately high in relation to its size. This concept has been further substantiated by the behavior of the cutaneous blood vessels in response to histamine. The facial vessels are most and the cutaneous vessels of the feet least sensitive to histamine. The reaction of the minute intracranial vessels to histamine indicates that the human cerebral blood vessels are equally or more sensitive to histamine than the facial vessels. Considering the relatively high position of the brain above the level of the heart in man, the sensitive vasomotor response of the cerebral vessels is in harmony with the concept formulated. Chemical substances, through their local action, may play a rôle in the physiologic and pathologic regulation of the cerebral circulation in man. Whether or not, in addition to the local chemical vasomotor regulation, nervous vasomotor regulation of the cerebral vessels is active in man is still an open problem, although observations on animals strongly suggest the existence of such a mechanism.

SUMMARY AND CONCLUSIONS

1. The minute cerebral blood vessels in man respond with dilatation to histamine.

2. The sensitivity of the human cerebral arterioles to histamine is unusually great.

3. The difference in the oxygen content between the arterial and internal jugular vein decreases during the administration of histamine, indicating an increased blood flow through the brain.

4. The vasomotor response of the cerebral vessels to histamine indicates that chemical substances, acting locally, may play a rôle in the physiologic and pathologic regulation of the cerebral circulation in man.

THE CLASSIFICATION OF GLIOMAS AND NEUROGLIA CELL TYPES*

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Prerequisite to an intelligent use of any classification of gliomas is a knowledge of the developmental and pathologic forms of neuroglia and of the behavior of neuroglia under various conditions. The classification suggested by Bailey and Cushing [1] is serving the purpose for which it was no doubt meant. It provides an excellent basis for selection and study. It is not necessary to employ all of the terms that these authors originally suggested, as was to be expected. The eight types indicated in the accompanying outline seem to be sufficient, at least for the present.

Some of the terms, namely, neuro-epithelioma, spongioblastoma multiforme, astrocytoma and ependymoma, were recognized as histologic subdivisions of the gliomas before the work of Bailey and Cushing. The additional four—medulloblastoma, astroblastoma, oligodendroglioma and unipolar (or better, polar) spongioblastoma—are subdivisions that were described for the first time under these titles in the classification of these authors.

This classification is familiar to neurologists. But more important than its form is its interpretation and application. It must be borne in mind that in the nervous system, cells in the spongioblastic series pass through a progressive development. There is no hard and fast line between the polar spongioblast and the astroblast, or between the astroblast and the astrocyte.

It is recognized that at birth large numbers of neuroglia cells have the form of astroblasts, and that a year later the astroblasts will have normally been transformed into astrocytes of the adult type. For the study of gliomas, however, it is not enough to understand the developmental forms. Pathologic forms of neuroglia cells are often seen in tumors. For example, in astrocytomas, astrocytes rarely have the normal star shape that they have in the brain. On the other hand, it is recognized that in the nervous system the disappearance of myelin is accompanied by the transformation of astrocytes from the star form into "piloid" astrocytes with long parallel fibers. It is not surprising, therefore, that in astrocytomas, in which the normal structure of nerve tissue

* Submitted for publication, March 25, 1931.

* Read before a combined meeting of the New York Neurological Society and the Neurological Section of the New York Academy of Medicine, March 10, 1931.

1. Bailey, P., and Cushing, H.: A Classification of the Tumors of the Glioma Group, Philadelphia, J. B. Lippincott Company, 1926.

is not present, the cells should tend to resemble piloid astrocytes and not the astrocytes of the normal cerebral tissue.

The classification has sometimes been used without intelligent understanding. For example, certain authors have discovered with surprise that different forms of neuroglia cells may be found in a single tumor. They must, of course, be familiar with the fact that that is a characteristic of spongioblastoma multiforme, a tumor to be considered by itself. If they also remember that neuroglial differentiation has no sharply distinct stages in the other gliomas, they will search only for the general stage of differentiation reached. They will then not be surprised to find that in an astroblastoma there may be some cells that

Gliomas	Synonyms
1. Neuro-epithelioma (Flexner)	Medullo-epithelioma and neuro-epithelioma (Bailey and Cushing)
2. Multiform spongioblastoma (Ribbert, Globus and Strauss)	Gliosarcoma (Borst), glioblastoma multiforme (Bailey and Cushing), polymorphous glioma (Roussy, Lhermitte and Cornil)[2]
3. Medulloblastoma (Bailey and Cushing)	Small round cell glioma, glioma sarcomatodes (Borst), pineoblastoma (Bailey and Cushing)
4. Oligodendroglioma (Bailey and Cushing)	Oligodendroblastoma
5. Polar spongioblastoma	Neurinoma centrale, unipolar spongioblastoma (Bailey and Cushing)
6. Astroblastoma (Bailey and Cushing)	
7. Astrocytoma (Golgi)	Astroma (Lenhossek)
8. Ependymoma	Ependymoglioma; ependymo-epithelioma, ependymoma and ependymoblastoma (Bailey and Cushing)

resemble polar spongioblasts and a few cells that have differentiated into astrocytes. They will then attempt to classify the tumor in question according to the general level of differentiation (always excepting spongioblastoma multiforme) and will stop impeding progress by unnecessary publications that hinder thoughtful neurologists in efforts to judge the classification from the point of view of its use in therapy and prognosis.

TYPES OF NEUROGLIA CELLS

It is possible to multiply indefinitely the number of names given to the stages in the development of neuroglia. A simple classification is adequate and is possible, owing to recent improvements in histologic technic. Neuroglia is developed from the neuroepithelium. It has nothing in common with that representative of the reticulo-endothelial system, microglia (fig. 1). Here again the work of certain observers, who seem to see in their sections a transformation of almost any type of cell into almost any other, must be ignored. These prolific authors,

2. Roussy, G.; Lhermitte, Jr., and Cornil, L.: Essai de classification des tumeurs cérébrales, Ann. d'anat. path. med.-chir. **1**:333, 1924.

some of whom are sincere if a trifle credulous, seem to see the transformation of connective cells into neuroglia cells, of neuroglia into nerve cells and of neuroglia into microglia. For such workers there can be no classification of tumors according to cellular type in the sense that Mallory has described it. These histologic atheists must create for themselves their own classification.

In gliomas, macrophages may be stained by microglial technic, just as they may be stained in tumors of all sorts in various parts of the body. These cells are apparently concerned only with the disposition of

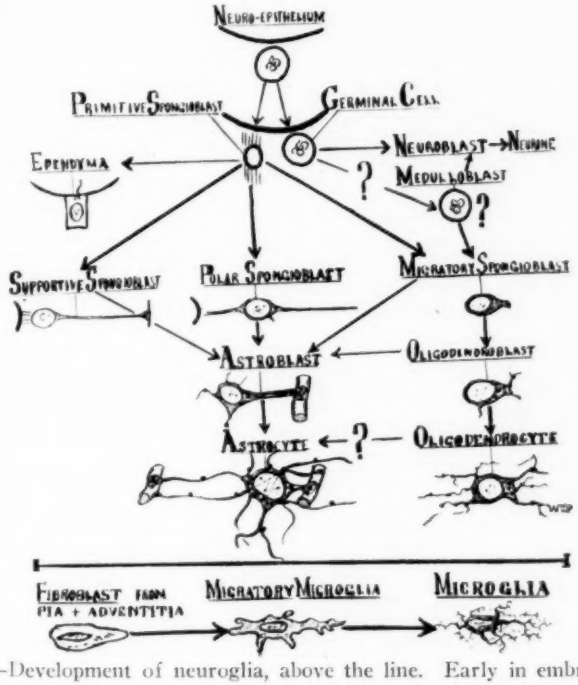

Fig. 1.—Development of neuroglia, above the line. Early in embryonic development and in organisms low in the embryonic scale, the primitive spongioblast produces the supportive spongioblast by attaching a cytoplasmic pole to the external limiting membrane and providing support even before the ingrowth of the vascular tree. At a somewhat later period, with the same parentage, the polar spongioblast wanders out into a more complex nervous system, the cell body perhaps moving, as has been suggested by O. Jones, along the peripheral expansion. Associated with the rapid formation of cells, the migratory spongioblasts, which are apolar having only a cytoplasmic nipple, leave the germinal epithelium to form both astrocytes and oligodendrocytes. The immigration of mesodermal cells to form microglia throughout the nervous system about the time of birth is schematized (after Penfield, Brit. M. J. **1**:337, 1931) below the line.

the products of destruction in a tumor. They engage actively in dendrophagocytosis, applying themselves to the expansions of large degenerating neuroglia cells. Tumors of the brain are not formed by microglia.

The neuro-epithelium gives rise to spongioblasts, which eventually develop into neuroglia, and to neuroblasts which form the ganglion cells (fig. 1). Both cellular forms wander through the nervous system to take their proper places, guided by some strange tropism. Schaper suggested that there was an indifferent cell which, after wandering out, might develop either in the one direction or in the other. This cell, which Bailey and Cushing called a medulloblast, has only a theoretic existence. Cajal could not find histologic evidence of it in his extended studies of embryology. I have never seen a medulloblast, and cannot therefore recognize this cell in a tumor, although many pathologists speak with facility of medulloblasts, deriving their knowledge of embryology from neoplastic tissue.

For the purposes of recognition in tumors, a simpler outline may be used. Two forms of spongioblasts may be designated (fig. 2). The polar spongioblast, which grows out from the epithelium with one or more polar expansions to become presently attached to a blood vessel or to pia, develops by a natural transition into the astroblast, as shown in figure 2. Neuroglia fibrils appear early in astroblasts, and a proportional shortening of the perivascular expansion results in the appearance of the adult astrocyte. On the other hand, the apolar spongioblast or migratory spongioblast is produced in great numbers at the time of the appearance of oligodendroglia in the nervous system. Without developing long polar expansions, these cells, by a natural transformation, form oligodendroblasts and oligodendrocytes. It is likely that either type of spongioblast may form astrocytes or oligodendroglia, but this description indicates the two great lines of development in the spongioblastic series.

The neuro-epithelium is gradually transformed into the ependyma of the adult nervous system.

SUBDIVISIONS OF GLIOMA

The form of neuroglia cells depends on the environment in which they grow. The astrocyte that finds itself in the gray matter does not form neuroglia fibrils, except under pathologic conditions. The astrocyte that finds itself in the white matter grows larger and forms neuroglia fibrils normally. An adult neuroglia cell that grows in a more or less pure culture of such cells has little resemblance to the normal protoplasmic neuroglia cells. I have never seen a true protoplasmic astrocytoma and cannot conceive of the growth of normal protoplasmic astrocytes except under conditions somewhat similar to those that obtain in the gray matter.

The Astrocytoma.—The typical cell of this tumor is a fiber-forming cell, with few vascular attachments, the fibers of which are apt to be long and often parallel. To find the analog of such astrocytes one must

turn to the dorsal columns in a case of tabes dorsalis in which the myelin and oligodendroglia have disappeared. Here the astrocytes are represented by cells that may be best called piloid (hairlike) astrocytes, as illustrated in figure 2. The same type of astrocyte appears in the brain in very old scars from which myelin and nerve fibers have disappeared. Star shaped astrocytes may appear but are the exception, not the rule.

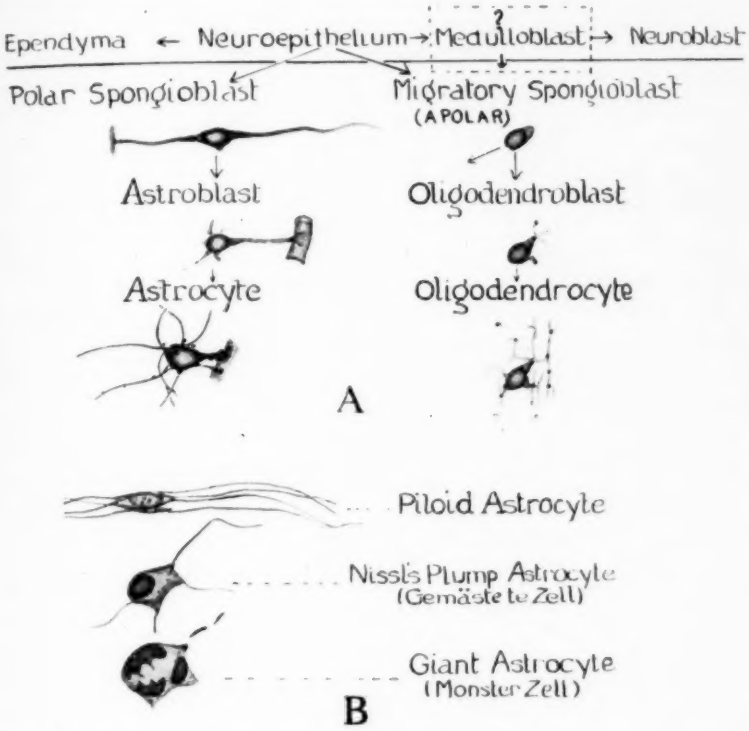

Fig. 2.—An outline of the more important neuroglial types encountered in neoplasms. *A*, developmental. The two chief lines of development are indicated. This cleavage is not hard and fast, and cross development probably occurs. *B*, pathologic. The piloid (hairlike) astrocyte is the glia replacement cell. After the disappearance of myelin, as in sclerosis of the dorsal columns and in old areas of injury to the brain, in which nerve fibers are practically absent, as in old injuries received at birth, piloid cells appear. They are not found in normal neural tissue. The gemästete cell is formed by an enlargement of the cellular body of an astrocyte which becomes filled with a homogeneous opaque fluid. Nissl called it the "fed-up" cell or, better, the plump astrocyte. It appears in the brain as the result of chronic pathologic conditions. A further evolution of the plump astrocyte results in the giant astrocyte. Its expansions, which may be long and fibrous, tend to degenerate and disappear. Inefficient effort at cell division results only in the multiplication and alteration of the nucleus. Chronic deprivation of oxygen will produce these bizarre forms in the brain. At times they succeed in complete subdivision both in the nervous system and in tumors.

The tumors that have been called protoplasmic astrocytomas have often contained cells which, owing to a pathologic influence—probably a decrease in blood supply—resemble Nissl's gemästete cells (fig. 2). As these cells continue to evolve, they may occasionally form giant cells, such as are seen in figure 2, with a gradual loss of their fibrous expansions.

Particularly in view of the fact that there seems to be little difference in the period of survival, the astrocytomas may be taken together as one group without subdividing them into protoplasmic and fibrous tumors. Fortunately, these tumors form the largest single group under the heading of glioma. To belong to this group a tumor must have for its typical cell the astrocyte, which is usually found in the piloid form.

The Oligodendroglioma.—This tumor is made up of cells with rounded nuclei, the protoplasm of which is difficult to stain. Gold chloride stains show astrocytes scattered through the tumor. These astrocytes often seem to form a stroma for the tumor and are occasionally protoplasmic. They are usually of the normal adult form. The tumors are rare, and my experience is limited to half a dozen. Oligodendroglia cells are rarely present. As a rule, the typical cell seems to be less differentiated, and the tumor group should no doubt be called oligodendroblastoma. Calcium is readily deposited in these tumors, sometimes even in the presence of rapid growth. Many cells are found the form of which is that of the migratory spongioblast. These tumors seem to be capable of transformation from slow to rapid growth with the appearance of numerous mitotic figures.

The Ependymoma.—In the diagnosis of these tumors, in my opinion, too much has been made of the blepharoplasten or centrosomes that are found at the base of cilia, which the ependymal cells may form. It seems unnecessary to have the two subdivisions, ependymoblastoma and ependymoma. For classification in this group, there need be only the formation of organized ependymal structure at some place in the tumor. The studies of Kernohan [3] at the Mayo Clinic showed how variously ependymomas may develop when they arise in the spinal cord and cauda equina. In some of these tumors, the tendency for the cells lining the ependyma to form peripheral expansions, which become attached to septums of connective tissue or to blood vessels, is marked. Such ependymal cells may be classed as supportive spongioblasts, but the tumors have areas of true ependyma formation. As one would expect, many ependymomas have cells not immediately adjacent to the epithelial structure that have developed the form of polar spongioblasts, or fully

3. Kernohan, J. W.: Primary Tumors of the Spinal Cord and Intradural Filum Terminale, in Cytology and Cellular Pathology of the Nervous System. New York, Paul B. Hoeber, 1931.

developed astrocytes; but here again the astrocyte is not apt to resemble the astrocyte of the normal cerebral tissue, for it is of the neoplastic type.

The Astroblastoma.—I shall next consider the tumors in which the type cell is less differentiated. The astroblastoma is characterized by the arrangement of cells about blood vessels and septums of connective tissue. This may be recognized with nonspecific stains. When a specific silver stain is successful, long expansions will be found from the body of the cell to the vessel or septum. The outstanding characteristic of an astroblastoma is this arrangement. These tumors have been unnecessarily confused with ependymomas. The latter must show ependymal epithelium. In areas not adjacent to blood vessels, polar spongioblasts are often found, as is to be expected, and some cells that may be classed as astrocytes. One must not demand a pure culture of neoplastic cells in a tumor of this type.

The Polar Spongioblastoma.—This title should obviously be applied to the unipolar spongioblastoma, as the cells may have any number of polar expansions. At first glance, these tumors may be confused with astrocytomas. A careful technical study, however, reveals the fact that they do not form neuroglial fibrils. Instead, the structures that at first sight may be taken for fibrils are found to be long tails of the cells themselves. These tails are occasionally attached to a blood vessel or some connective tissue structure. My limited clinical experience with these tumors would indicate that they grow more slowly than the astroblastomas. This type of spongioblast is obviously a more differentiated one than the apolar or migratory spongioblast, and in consideration of that fact it is not surprising that the more rapidly growing embryonic tumors should contain apolar spongioblasts.

The Medulloblastomas.—Analysis of this type of tumor is a more difficult problem. That they form an easily recognized and distinct group should be accepted. The name was suggested by the belief that the type cell was an indifferent one capable of developing into either a neuroblast or a spongioblast, because neuroblasts were apparently seen in these tumors. In the tumors that have formed a part of our collection I have never found neuroblasts, and the morphology of medulloblasts in the nervous system is unknown.

The outstanding histologic characteristics are that the cells are closely placed, the nuclei are for the most part round, the protoplasm is rather difficult to stain, and the cells are arranged in hollow balls that in cross-section appear like rosettes. These tumors do not differentiate up the embryologic scale. There is often a well developed stroma of connective tissue. From a morphologic point of view, they resemble apolar spongioblasts. As already indicated, I have grave

doubts as to whether or not the cells in this tumor are medulloblasts. The tumor might have been called an apolar spongioblastoma. It is important, however, to adhere to one terminology with an adequate understanding of what the names mean, and medulloblastoma is now a well recognized tumor. Its histologic structure is altered markedly by roentgen therapy.

The Neuro-Epithelioma.—This tumor may appear in the retina, the central nervous system or a peripheral nerve. It is characterized by the formation of rosette-like reproductions of the neuro-epithelium. It is the only type of glioma that has a tendency to widespread metastasis, but this is not an invariable accompaniment. There is little differentiation in this tumor.

The Spongioblastoma Multiforme.—This type must be considered apart from the other tumors. The outstanding histologic characteristic is the appearance of the blood vessels, which grow rapidly. There may be both endothelial and adventitial proliferation. Glomeruli of tissue often form on them, and mitotic figures are found in cells of the walls of the vessels. This overgrowth of vascular tissue results frequently in a closure of the lumina of the vessels and must produce a rapid increase and decrease in vascularization of the various areas of the neoplasm. These tumors are sometimes multiple, a further evidence that the underlying essential phenomenon in their production is the change of the blood vessels. Near such tumors in the brain I have also seen the same vascular alteration in the cerebral blood vessels.

It is impossible to describe a type cell in these tumors. Globus and Strauss [4] pointed out three forms of cell that appear most frequently: (1) the giant cell, which is indicated in figure 2 and is formed as a result of chronic deprivation of blood supply to the brain; (2) a pyriform cell, which may be considered to coincide in general with Nissl's plump cell, and (3) small cells with a small amount of cytoplasm and a round nucleus. Histologically, the small cells resemble apolar spongioblasts. The irregularity in the form of the cells, the scattered areas of necrosis and the presence in these tumors of neuroglia cells of all types and stages of development are probably to be explained by the irregularities of vascularization consequent on the hyperplasia and destruction of the blood vessels.

The name spongioblastoma multiforme is descriptive, whether one believes that the true type cell is the apolar spongioblast or not. The name, polymorphous glioma, suggested by Roussy, Lhermitte and Cornil,[2] is also descriptive. It seems best, however, to adhere to the

4. Globus, J. H., and Strauss, I.: Spongioblastoma Multiforme, A Primary Malignant Form of Brain Neoplasm; Its Clinical and Anatomic Features, Arch. Neurol. & Psychiat. **14**:139 (Aug.) 1925.

name that was given to this tumor by Globus and Strauss who first clearly described in detail the neoplasm as an entity.

The substitution made recently by Cushing and Bailey of glioblastoma multiforme has little in its favor. It does not clarify the conception of the tumor. No such cell as a glioblast has ever been described in embryologic studies, and the use of this term tends to cause confusion in the study of the tumors according to the outline that they themselves originally suggested. Such a change in terms should not be accepted unless it definitely clarifies one's conception of the tumor. Unless care is exercised, neurologists will tend to give their own favorite names to each tumor and, like the workers in the Tower of Babel, will cease to speak the same language.

COMMENT

The classification of gliomas that I have discussed is, with certain slight modifications, that adopted by the American Neurological Association in its official terminology. It represents a simplification of the classification of Cushing and Bailey. If one sets aside the spongioblastoma multiforme as a tumor with its own peculiarities, the classification follows in general the development of the spongioblastic series (fig. 2). The neuro-epithelioma is the most elementary. The polar spongioblastoma, the astroblastoma and the astrocytoma correspond with stages in the normal development of the astrocyte from the polar spongioblast, while, on the other hand, the medulloblastoma and the oligodendroglioma (oligodendroblastoma) correspond with the development of the oligodendroglia from the apolar spongioblast. In my experience, the malignancy of these tumors generally corresponds inversely to the differentiation of the cellular type.

The "acid test" that must be applied to any classification is whether or not it serves as a basis for the intelligent prognosis and treatment of tumors. If it does, it has achieved its purpose. Whether one fancies the name already attached is of little importance, but the recognition of biologic entities under whatever name is of the utmost importance to those who, for the patient, must face the specific problem of a glioma of the brain or of the spinal cord.

THE NEURO-ANATOMY IN RESPIRATORY FAILURE

REPORT OF TWO CASES *

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Present knowledge and understanding of the fiber tract pathways and nuclear masses in the central nervous system which have to do with the conduction and integration of respiratory impulses is still somewhat uncertain, in spite of the considerable amount of research that has been done. One of the main obstacles to the solution of this problem has been the inability of workers to produce small localized lesions in experimental animals. Focal lesions of the desired location are of the utmost importance when a variety of functionally different nuclear masses and fiber tracts are crowded together in as small a structure as the brain stem. A large part of the experimental work with animals on the location of the central nervous respiratory system has involved lesions affecting one third, one half or complete sections of the brain stem. Obviously, these lesions destroy tracts and nuclear masses that have little or nothing to do with the conduction of respiratory impulses, and consequently produce a complicated picture which cannot be clearly interpreted.

Therefore, any localized lesion that has been associated with respiratory failure should be a real contribution to the study of this complex problem. The cases herein reported are of this nature. Although it should be understood that they by no means solve the problem at hand, they are extremely suggestive and should give a clue for further experimental work.

For some time there was doubt in my mind whether the cases presented could truthfully contribute to this study, because of unexpected clinical and anatomic complications. It was only after a thorough and critical review of the literature on the nervous respiratory system that it was felt justifiable to describe the cases from the standpoint herein reported. Because of this, an attempt has been made to be inclusive, thorough and, at the same time, brief in the review of the research work on this problem.

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PHYLOGENETIC DEVELOPMENT OF THE RESPIRATORY MECHANISM

In the simpler forms of life, such as plants, oxygen is absorbed from the surrounding gaseous medium through the exposed surfaces. In the lower forms of animal life, oxygen is taken into the body cells without the use of a true respiratory mechanism. This type of breathing would be essentially non-nervous. As one ascends the animal scale, the respiratory mechanism is complicated by a nervous apparatus.

In insects, the result is obtained by a system of air tubes which ramify among the tissues and supply oxygen directly to the functioning cells.[1] Brown and Roller,[2] experimenting with the central nervous system of Acridiidae, especially that of the grasshopper, found that the insect can be divided into several breathing segments, each division having a definite rhythm and force of action and each consisting of simple afferent and efferent reflex nervous paths by which respiratory impulses are conducted. In most water-breathing animals, a portion of the body surface is lamellated, vascularized and innervated to form gills which facilitate the absorption of oxygen by the blood stream. Hyde,[3] while working on the respiratory mechanism in Limulus, demonstrated that each body segment associated with breathing contained a ganglion which acted as a relay station for the sensory and motor nerves carrying respiratory impulses of the corresponding segment. Any number of these ganglionic stations could be isolated, not only from one another but also from the rest of the central nervous system, without losing their integrity in function. He concluded from these experiments that a superior center controlling the coordination of the segmental ganglia in carrying out the respiratory function does not exist in Limulus. In a later work on the localization of a respiratory center in the skate, Hyde[4] demonstrated a definite transitional stage in the development of the respiratory nervous system, between that found in Acridiidae and Limulus and that found in the higher forms of animal life. He believed that in the skate all the respiratory centers were located in the caudal half of the medulla oblongata (fig. 1). These centers consisted of isolated nuclear masses, each controlling a unit of the respiratory organs. Although these nuclear masses could function as independent units, the respiratory rhythm became greatly disorganized when they were isolated

1. Herrick, C. J.: Introduction to Neurology, Philadelphia, W. B. Saunders Company, p. 265.

2. Brown, O. H., and Roller, L. W.: The Effects of Gases and Pressure upon the Respiration in the Acridiidae, Sc. Bull., 1904, no. 1.

3. Hyde, I. H.: Nervous Influences on the Respiratory Mechanism in Limulus, J. Morphol. **60**:347, 1894.

4. Hyde, I. H.: Localization of Respiratory Center in the Skate, Am. J. Physiol. **10**:236, 1903.

from one another. He concluded from these observations that in the skate there is an attempt at centralization and coordination of the respiratory units.

In the air-breathing vertebrates, lungs are developed to accomplish the aeration of the blood. Here a much more complicated structure is

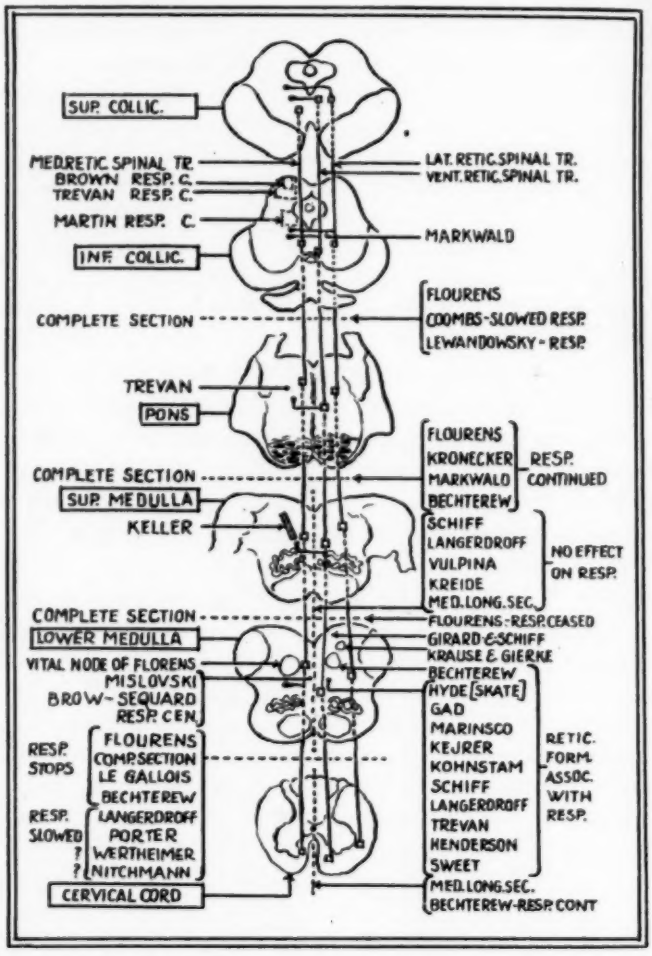

Fig. 1.—Localization of the nervous respiratory mechanism as pointed out by experimental workers on this problem.

involved, including both visceral and somatic musculature and nervous structures. A centralized nervous apparatus is developed to coordinate a complexity of afferent and efferent respiratory nerve paths.

From this brief discussion of the phylogenetic development of the breathing mechanism, certain generalized conclusions can be made in

regard to animals with a nervous controlled respiration. The invertebrate form differs in two main respects from that of the vertebrates: 1. The respiratory system of the lower forms is a segmental structure, each segment functioning independently of the others. In the vertebrates the respiration in general functions as a unit, for the nervous system involved is a much more complicated mechanism which necessitates unification. 2. The respiratory mechanism of the invertebrates is essentially a visceral structure, while that of the vertebrate is a somatic structure on the motor side, the visceral structures playing a part only on the afferent side.

THE PERIPHERAL AFFERENT AND EFFERENT PATHS OF THE RESPIRATORY NERVOUS MECHANISM

The more important nerves involved in the conduction of afferent impulses for respiration are the thoracic and cervical dorsal roots, the vagus, the glossopharyngeal and the trigeminal. Coombs [5] studied the part played by the dorsal roots in respiration by sectioning them in cats. She showed that section of the dorsal roots caused slowing and finally a cessation of costal respiration. Section of both thoracic and cervical nerves resulted in a more marked slowing and alteration than section of the thoracic roots alone. Further evidence brought out in her experiments was that section of the dorsal roots, following a similar lesion through the posterior corpora quadrigemina, produces no more changes than section of the posterior corpora quadrigemina alone (fig. 1). This was also shown to be true by Sherrington,[6] who confirmed the work of others in his experiments and concluded that certain fibers of the dorsal roots have end-stations at some point in the midbrain. Barry,[7] from experiments on cats and rabbits, concluded that during ordinary inspiration impulses pass to the respiratory center by way of the dorsal roots to the spinal cord, traveling via the somatic nerve fibers; also that inspiratory impressions of pulmonary origin pass to the stellate ganglion, to white rami and up the spinal cord.

The vagus afferent fibers concerned with respiration originate from the parenchyma and pleurae of the lung (Ranson [8]), the cells of which lie in the ganglion nodosum. From here fibers of cells of the nucleus solitarius arise. Fibers of this tract are said to ascend and descend in

5. Coombs, H. C.: Relation of the Dorsal Roots of the Spinal Nerves and the Mesencephalon in the Control of Respiratory Movements, Am. J. Physiol. **46**:459, 1918.

6. Sherrington, C. S.: The Integrative Action of the Nervous System, New York, C. Scribner's Sons, 1906.

7. Barry, D. T.: J. Physiol. **45**:473, 1913.

1921.

8. Ranson, S. W.: Afferent Paths for Visceral Reflexes, Physiol. Rev. **1**:477.

the reticular formation to make connections with the various visceral and somatic nuclei of the midbrain, medulla oblongata and upper cervical cord (Tilney and Riley,[9] and Allen [10]). According to the theory of Herring and Brever,[11] there are two types of vagus fibers, inspiratory and expiratory, which are stimulated alternately by the expansion and collapse of the lungs. The theory further states that stimulation of the expiratory fibers works through the respiratory center to limit the extent of inspiration and initiate expiration. It is probable, however, that only one type of fiber is carried by the vagus which limits inspiration and initiates expiration. This idea is supported by the work of Head,[12] Schenck,[13] Einthoven,[14] Nickolaides [15] and Sjablonn.[16]

Impulses from the pharynx, larynx and trachea pass via the glossopharyngeal, superior laryngeal and recurrent nerves to terminate also in the nucleus associated with the tractus solitarius. These nerves, when stimulated, lead to inhibition of respiration in the expiratory position.[8] In swallowing, respiration is inhibited by afferent impulses from the pharyngeal mucosa passing via the glossopharyngeal nerve. Irritation of the nasal mucous membrane produces the same results (Mayer, Magne and Plantefol [17]). These impulses pass via the trigeminal, synapsing in the ganglion of the peripheral nerve to terminate around cells giving rise to the sensory tract of the fifth cranial nerve in the brain stem. Painful pressure on the eyeball also causes alteration in respiration (Petzetakis [18]), these impulses likewise passing via the fifth cranial nerve. Tactile stimulation produces increased expiration, and a sharp stimulation brings respiration to a standstill in expiration.

On the efferent side, the following nerves carry impulses to the muscles associated with breathing: phrenic nerve, intercostal nerves and recurrent laryngeal, glossopharyngeal, hypoglossal, trigeminal and facial nerves.[9] The phrenic nerve supplies the chief muscle of respiration, the diaphragm; this nerve arises from the third, fourth and fifth cervical segments of the spinal cord. The intercostal nerves supply the second most important muscles of respiration, the intercostals, together with the

9. Tilney and Riley: The Form and Functions of the Central Nervous System, New York, Paul B. Hoeber, Inc., 1923.

10. Allen, W. F.: Respiratory Pathways in the Spinal Cord, J. Comp. Neurol. **43**:451, 1927.

11. Herring and Brever, quoted by Ranson (footnote 8).

12. Head, H.: Brain **16**:1, 1893.

13. Schenck, F.: Arch. f. d. ges. Physiol. **100**:337, 1903.

14. Einthoven, W.: Quart. J. Exper. Physiol. **1**:243, 1903.

15. Nickolaides, R.: Arch. f. Physiol., 1914, p. 553.

16. Sjablonn, J. C.: Skandinav. Arch. f. Physiol. **42**:450, 1917.

17. Mayer, A.; Magne, H., and Plantefol, L.: Compt. rend. Soc. de biol. **170**: 1347, 1920.

18. Petzetakis, M.: J. de physiol. et de path. gén. **16**:1927, 1914-1915.

accessory muscles of respiration. The recurrent laryngeal nerve supplies the less important arytenoid muscles and vocal cords. The twelfth cranial nerve supplies the depressor muscles of the tongue, while the ninth, seventh and fifth cranial nerves supply respectively the muscles of the pharynx, nares and lower jaw.

The foregoing description of the large number of muscles and nerves involved in the respiratory act is given in order to visualize the importance of a central coordinating integrative nervous mechanism for the proper functioning of this complex neuromuscular structure. The pages immediately following will be given over to a discussion of the theories, past and present, concerning this controlling respiratory nervous mechanism.

THE CENTRAL NERVOUS RESPIRATORY MECHANISM

Cerebral Hemispheres.—That the cerebral hemispheres may play a part in the control of respiration cannot be denied, as any one may at will regulate the rhythm and rate of breathing within certain limits. Winkler,[19] in carrying out some experiments on attention and respiration, showed that concentration causes a shortening of the time of expiration, which at the same time becomes more superficial; the same holds true, to a lesser degree, for inspiration. When attention is released, a compensating retardation of respiration sets in. Langelaan and Beyerman,[20] while experimenting on dogs, found a small area at the top of the sigmoid gyrus which when stimulated caused an acceleration and deepening of the respiration, whereas extirpation of this part of the brain caused temporary retardation and irregularity of the respiratory movements. They assumed that compensation was carried out by lower centers. Beyerman [21] in his researches went so far as to conclude that this area could be divided into two parts, stimulation of one causing a retardation of respiration and stimulation of the other an acceleration. It may be concluded, however, that the part played by the cerebral hemispheres in respiration is essentially voluntary. They are not a vital part of the nervous respiratory mechanism. That this is true has been shown many times by various workers who have sectioned the brain stem above the superior corpora quadrigemina and have obtained only temporary changes which disappeared immediately after recovery from the shock.

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19. Winkler, F.: Attention and Respiration, Proc. Roy. Acad. Sc., Amsterdam, 1898, p. 133.

20. Langelaan, J. W., and Beyerman, D. H.: Localization of a Respiratory Center in the Frontal Lobe, Brain **26**:81, 1903.

21. Beyerman, D. H.: Proc. Roy. Acad. Sc., Amsterdam, 1899.

Midbrain.—There is considerable disagreement as to the part played by the midbrain in respiration. Flourens [22] (1842-1851) was probably the first to carry out experiments on this particular problem. He began his experimental procedures by removing the cerebrum, cerebellum, corpora quadrigemina, pons, medulla and cervical cord segments, one after the other, in a caudal direction on rabbits and pigeons. Respirations persisted until sections were made through the medulla oblongata, when they ceased (fig. 1). He made no statement as to any changes taking place after section of the posterior corpora quadrigemina. Newell Martin [23] later found an area deep in the midbrain of the rabbit, lying beneath the posterior quadrigeminal body (fig. 1) and close to the aqueduct, which he described as a respiratory regulating center, which was similar to that in the corpora bigemina of the frog. Electrical stimulation of this center caused acceleration of the inspiration, which finally passed into a tetanic fixation of the chest in an expiratory condition and correspondingly diminished or altogether inhibited expiration. Marckwald [24] (fig. 1) suggested a center in the midbrain which in some manner regulates respiration and probably lies in the reticular formation at the level of the posterior colliculi. Brown [25] stimulated a small area at the level of the anterior corpora quadrigemina, just over the tectobulbar tract and 3 mm. to one side of the aqueduct, and obtained gasping and panting movements. He found this response over an area only 1.5 mm. square (fig. 1). He suggested that the tectobulbar tracts connect the centers in the midbrain with the lower medulla. Trevan,[26] in 1916, working on the respiratory mechanism in the midbrain, concluded that when the posterior quadrigemina are intact there is no change in the carbon dioxide alveolar tension, while it is increased when the posterior colliculus is sectioned at its caudal end. From this observation he believed that the respiratory mechanism is less sensitive to changes of p_H when only the medullary centers are intact. He therefore described a center in the lower midbrain region, which he localized lateral and dorsal to the aqueduct (fig. 1). The observations of these last two workers, Brown and Trevan, more or less confirm Martin's results. Coombs,[5] working with cats, sectioned the brain stem caudal to the anterior colliculus and obtained a slower, deeper form of respiratory movement which she described as similar to the most severe effect that follows double vagotomy. Coombs and Sherrington have brought

22. Flourens, M. J. P.: Recherches expérimentales sur les propriétés et les fonctions du système nerveux, ed. 2, Paris, Crevot, 1848, p. 173.

23. Martin, Newell: J. Physiol. **1**:370, 1878-1879.

24. Marckwald, B.: Ztschr. f. Biol. **5**:149, 1887.

25. Brown, T. G.: Respiratory Tract in the Mid-Brain, J. Physiol. **48**:xxxii, 1914.

26. Trevan, J. W.: J. Physiol. **50**:xliii, 1916.

forward considerable evidence that fibers of the posterior roots carry afferent impulses from the lungs and have end-stations at some point in the midbrain, for, as Coombs pointed out, section of the dorsal roots of the spinal nerves after section into or behind the posterior corpora quadrigemina produced no more change in the quality of respiration than a section of the posterior corpora quadrigemina alone (fig. 1).

In summary, it is to be noted that most workers agree that the midbrain has a definite place in the regulation of the respiratory movements. Further, Marckwald inferred that the midbrain is only one part of this regulatory nervous system. Martin, Marckwald, Trevan and Brown all agreed in an area located near the aqueduct; others obtained modified respiratory movements by sectioning the midbrain at its caudal end; Coombs, Marckwald, Lewandowsky and others obtained a slowing of respiration after making such a lesion.

Pons.—Trevan [27] described a region in the cephalic pons that is sensitive to direct chemical stimulation of the blood (fig. 1). In contrast to this he held that the bulbar level is concerned with vagal impulses. Keller,[28] working on the localization of the polypnea center in cats by making partial medial and lateral sections of the brain stem at the level of the pons and cephalic medulla, believed that such a point lies somewhere in the lateral region of the cephalic part of the pons. Keller's experiments are of unusual interest in that he was one of the first to study the respiratory nervous mechanism by making only partial sections of the brain stem. Lumsden [29] described four respiratory centers located in the pons and medulla oblongata, as follows: (1) a center at the cephalic part of the pons which maintains a normal respiratory rate by periodically inhibiting apneusis; (2) an apneustic center at the level of the striae acusticae which gives rise to respiratory tonus (apneusis)—he believed that vagus stimulation inhibits this center and that carbon dioxide stimulates it; (3) an expiratory center just caudal to the striae acusticae, and (4) a gasping center at the level of the middle and lower thirds of the medulla oblongata. Lumsden further found that a lack of oxygen stimulates this center, while the vagus stimulates it when the more cephalic centers have been removed. If these are intact, the effect of the vagus on the gasping level alone changes, as the nerve acts more powerfully on the upper centers. The cephalic levels, when intact with the gasping center, have an inhibitory effect on the latter.

27. Trevan (footnote 26). Trevan, J. W., and Brock: The Effect of Section of the Vagi on the Respiration of the Cat, J. Physiol. **56**:331, 1922.

28. Keller, A. D.: Nervous Control of Respiration, Am. J. Physiol. **89**:289, 1929.

29. Lumsden, T.: Observations on Respiratory Centers in the Cat, J. Physiol. **57**:153 and 355, 1923; Regulation of the Respiratory Center, ibid. **58**:80 and 111, 1923.

Although Lumsden does not localize the respiratory nervous mechanism to any one region, he divides four centers and crowds them into a relatively small part of the brain stem. He seems to have overlooked a large part of the early work on this problem. Henderson and Sweet,[30] in a recent paper, did not agree with Lumsden. They believed that Lumsden's upper apneustic center is the result of decerebrate rigidity from the sectioning of the rubrospinal tract at the level of this tonic center. Henderson and Sweet showed that, after cutting both vagi, apenusis could be produced by a midline section through the decussation of the rubrospinal tract. In other words, apneusis is due to a tonus-producing activity of medullary centers when they are unaffected by impulses coming from the red nucleus.

Contrary to the results of the workers cited, Kronecker and Bechterew [31] claimed that they obtained no essential changes in the respiratory movements when the medulla oblongata was separated from the pons (fig. 1).

It is difficult to accept the results of Kronecker and Bechterew in the light of other workers. If section of the midbrain from the pons modifies respiration, it is extremely difficult to believe that section of the pons from the medulla would not also modify the respiratory movements. The work of Keller [28] would lead one to believe that in the pons is a fiber-conducting system for respiratory impulses between the midbrain and medulla and cord, which plays no essential part in the integration of the respiratory impulses in a direct manner.

Medulla Oblongata.—Most of the experimental work on this problem indicates that the main coordinating nervous level of respiration is located in the medulla, and consequently a considerable amount of work has been carried out in an attempt to define and localize clearly this bulbar respiratory mechanism.

It was known as far back as the time of Legallois (1824)[32] that section of the brain stem below the medulla oblongata produced a marked modification in the respiratory movements (fig. 1). Bechterew [31] claimed that because respiration is not greatly influenced by separation of the medulla from the pons the chief center must lie in the bulbar portion of the brain stem. That such an area exists is further shown by the fact that cutting the vagi produces a marked modification in breathing. The respirations become slow, inspiration appears spastic and the expiratory pause is greatly prolonged, the respiratory movements being aided by the abdominal muscles. The breathing capacity is decreased, and the animal often dies as a result of insufficient exchange of gases.

30. Henderson, V. E., and Sweet, T. A.: The Respiratory Center, Am. J. Physiol. **91**:94, 1929.

31. Bechterew, W. V.: Die Functionen der Nervencentra, Jena, Gustav Fischer, 1908, part 1.

32. Legallois: Expériments sur la principe de la vie, 1812, p. 160.

It is well known that a section through the lower end of the medulla oblongata destroys the thoracic breathing, but does not influence the respiratory movements of the face and larynx.

Legallois [32] and Flourens,[22] early in the nineteenth century, showed that damage to the medulla at the level of the calamus scriptorius resulted in paralysis of the respiratory movements. Such a lesion also resulted in cessation of the heart movements. As a result of the experiments of these two early workers, this area beneath the caudal end of the floor of the fourth ventricle became known to later workers as the vital node of Flourens (fig. 1, lower medulla). Flourens [22] described this vital node as being the size of a pinhead and situated on both sides of the median raphe just above the level of the calamus scriptorius, in the depth of the dorsal part of the reticular formation near the sensory nucleus of the vagus (fig. 1). Girard [33] and Schiff [34] localized a like area near the ala cinerea (fig. 1, lower medulla). Gierke [35] and Krause localized it in the gray substance of the fasciculus solitarius of the medulla oblongata (fig. 1, lower medulla). Gierke could not find the nerve cells described by Flourens in his vital node and so, on the basis of his own experiments, placed the point in question near the tractus solitarius. Girard,[33] along with others, did not consider the fasciculus solitarius as a respiratory center but rather as a descending respiratory pathway. This tract is occasionally described as Gierke's tract. Anatomically, the fasciculus solitarius is well known to represent the descending root of the vagus and glossopharyngeal nerve (Tilney and Riley). It has been shown that this tract can be destroyed without interference with the respiratory movements (Bechterew,[31] Mislavski,[36] Gad and Marinesco [37]). Holm [38] attempted to localize the respiratory center in the ventromedial part of the dorsal nucleus of the vagus, but obtained negative results. Brown-Séquard [39] denied the existence of a vital node and was inclined to accept the localization of the respiratory center in the dorsal part of the reticular formation. He assumed that this so-called center in the medulla had an inhibitory influence on

33. Girard, H.: Mém. Soc. de phys. de Génève, 1890, suppl. 4.

34. Schiff, M.: Einfluss des velangerten Marks auf die Athmung, Arch. f. d. ges. Physiol. **3**:624, 1870; **4**:225, 1871.

35. Gierke, V. O. G.: Die Theile der Medulla oblongata, deren Verletzung die Athembewegungen hemmt, und das Athemcentrum, Arch. f. d. ges. Physiol. **7**: 583, 1873.

36. Mislavski, N. A.: Ueber das Athmungzentrum, Dissert., Kasan, 1884.

37. Gad, J., and Marinesco, G.: Ueber das Atmungzentrum in der Medulla oblongata, Arch. f. Physiol, 1893, p. 175.

38. Holm, H.: Arch. f. path. Anat. **131**:78, 1893.

39. Brown-Séquard, C. E.: Course of Lectures on the Physiology and Pathology of the Central Nervous System, delivered at the Royal College of Surgeons in May, 1858; Philadelphia, 1860.

breathing, his opinion being that on pricking an area in the dorsal reticular formation of the bulb, respiratory movements were abolished not through a destruction of the region in question, but solely through a mechanical irritation of it. The respiratory center, as Brown-Séquard understood it, is of large size. He localized it as extending from the cervical cord upward into the midbrain. Such a localization was also suggested later (1916) by Trevan,[26] who mentioned a region extending along the aqueduct caudad, following the floor of the fourth ventricle. Mislavski [36] described the respiratory center as a double nucleus of the medulla situated just beneath the calamus scriptorius in the depth of the reticular formation, partly outside and also inside the hypoglossal nucelus (fig. 1, lower medulla). Destruction of this region by means of pricking stopped the respiratory movements immediately. Electrical stimulation of this area by Mislavski resulted in a more rapid respiratory rate. Gad and Marinesco [37] claimed that the various centers already described, with the exception of those of Brown-Séquard and Trevan, could be destroyed without the respiratory movements ceasing. On the contrary, they found that the respiratory movements stopped at once if a piece of the gray reticular formation below and lateral to the hypoglossal nucleus was removed (fig. 1, lower medulla). Gad and Marinesco stated further that irritation of what they called the inspiratory tracts of the spinal cord or phrenic nucleus did not affect respiration in any manner, whereas irritation of the gray portion of the reticular formation just described produced each time a marked increase in expiration. The respiratory nucleus, as localized by Bechterew,[31] lies more lateral than medial to the hypoglossal nucleus. When he destroyed a small area of the gray matter above the calamus scriptorius, just lateral to the twelfth nucleus, he obtained each time a cessation of respiration. In accordance with these observations, Kohnstamm [40] found that after section of the spinal cord in its upper part he obtained a degeneration of the cells of the gray portion of the reticular formation on both sides of the twelfth nucleus in the same area in which Bechterew had removed and obtained cessation of respiratory movements. No degeneration of nerve cells was found in the facial or vagus nuclei. According to Arnheim,[41] the upper limit of the respiratory center is situated as high as the facial nucleus, which corresponds with the upper limit of the medulla. Irritation of this region in rabbits caused a contraction of nasal muscles, but had no influence on the other respiratory muscles. The nucleus reticularis of the raphe, which sends axons chiefly to the ventral part of the anterior lateral tract, can be cut vertically without any disturbance of respiration (Kohnstamm).

40. Kohnstamm, O.: Ueber die Koordinations-Kerne des Hirnstammes und ihre absteigenden Spinalbahnen, Monatschr. f. Psychiat. u. Neurol., 1900, p. 161.

41. Arnheim, K.: Beiträge zur Theorie der Athmung, Dissert., Berlin; Arch. f. Physiol., Leipzig, 1894, I.

According to Kohnstamm, the caudal portion of the respiratory nervous mechanism extends to the calamus scriptorius. He observed that irritation of this region often resulted in a tetanic contraction of the diaphragm and concluded further, for reasons which are not entirely clear, that the cells of the reticular formation are not the neurons of origin of the reticulospinal tract or "indirect respiratory neurons," but that they are the coordination cells of higher order for the expiratory mechanism. He believed that the formatio reticularis should be regarded as the vegetative regulatory center of the medulla oblongata, the most important being the respiratory regulatory mechanism which acts as a coordination level for the primary nuclei of the respiratory muscles.

Grossman [42] made the observation that after section of the brain stem between the facial nucleus and the vagus nucleus the respiratory movements of the nose stopped, while the remaining respiratory movements continued in a normal manner. On the contrary, a unilateral cut between the vagus nucleus and the phrenic nucleus of the upper cervical cord resulted in a discontinuance of the diaphragmatic movements on the injured side, while the respiratory movements of the nose and face continued. On these experiments he based his theory of a reciprocal associative respiratory center which governs the respiratory movements, in contrast to the belief in a joint center of the medulla oblongata which governs these several subcenters.

In consequence of Grossman's observations, Bechterew believed that, as Gad pointed out, stimulation of the so-called inspiratory tract of the cord, medulla and pons produces the same results, whether high in the phrenic nucleus, between this and the tenth or between the tenth and the sixth nucleus; all muscles dependent on the three levels are stimulated into activity. This, however, does not conform with Arnheim's [41] experiments. He found that by stimulation of the motor nucleus of the seventh nerve only the muscles of the nose responded. He noticed further that respiration was accelerated when an electrode was brought between the sixth nucelus and the calamus scriptorius, but only in case the electrode touched the gray portion of the formatio reticularis. His observations were confirmed by the experiments of Bienfait,[43] who observed rhythmic movements of the glottis when a cut was made between the sixth and tenth nucleus, and also between the tenth and the phrenic nuclei, this being contrary to the opinion of Grossman.

Kejrer [43] believed, from observation of a new-born infant with a perforation of the head, that the respiratory center must lie in the vital node of Flourens.

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42. Grossman, M.: Ueber die Athembewegungen des Kehlkopfes, Sitzungsb. d. k. Akad. d. Wissensch. math.-naturw. Cl., Wien **98**:385, 1889.

43. Quoted by Bechterew (footnote 31).

Schiff and Langendorff [44] believed this medulla respiratory mechanism to be bilateral, as one might expect, for on medial longitudinal section of the medulla oblongata respiration is not brought to a standstill but continues in a symmetrical manner (fig. 1). Stimulation, however, of the fifth or tenth nuclei on one side or the other produces an asymmetry of the respiratory movements.

Kreidl [45] made an interesting observation while experimenting on dogs, cats and rabbits. He made a medial longitudinal section through the medulla oblongata of these animals (fig. 1) and noticed that the movements of the alae nasi and vocal cords continued synchronously; they, however, became asymmetrical in action when the vagus of one side was cut beneath the point of origin of the inferior laryngeal nerve, indicating interference by vagal afferent pulmonary fibers and a consequent cessation of these pulmonary impulses.

Many investigators, from the results of experimental work, have inclined to a belief in a double respiratory center in the bulbar portion of the brain stem, i. e., an inspiratory and expiratory center. It is well known that chloral hydrate paralyzes inspiration, which suggests, but does not necessarily prove, a double respiratory nervous mechanism. Bechterew suggested that the weakening effect of the chlorals on inspiration is open to another interpretation, but he said nothing of the other hypothesis. He claimed that the observations of Mislavski [36] indicate conclusively the double nature of the nervous mechanism of breathing. However, it is difficult to find any definite data on this suggested double nervous structure. It has been said that the inspiratory and expiratory centers are stimulated by the varying constituents of the passing circulating blood and that they work alternately in action. Hering and Breyer, working with Bechterew,[31] believed that both the centers were stimulated and paralyzed alternately through the pulmonary branches of the vagus. In contrast to this is the fact that later workers doubt the existence of more than one type of vagal fiber. Peripheral stimulation excites in a specific manner the one or the other respiratory phase. Sudden cold stimulation of the cutaneous surfaces excites the inspiratory phase, while pain or irritation of the laryngeal mucus membrane excites the expiratory phase.

Spinal Cord.—Bechterew has observed in new-born animals (cats and dogs) that if the cord is sectioned just beneath the medulla (fig. 1), respiratory movements are sometimes seen which are explained as being carried out through the spinal centers. On the basis of experiments on young animals, Langendorff [44] maintained that the medulla oblongata acts as a regulatory apparatus which modifies the depth and frequency

44. Langendorff, O.: Einige neuere Untersuchungen über den Sitz des Athmungcentrums, Arch. f. Physiol., 1887, p. 237.

45. Kreidl, A.: Ueber das Athmungszentrum, Arch. f. Physiol., 1899, vol. 74.

of the respiratory movements. Disconnection of the upper brain stem from the cervical cord does not always stop respiration at once. Cessation of respiration is claimed by Langendorff to result as a consequence of stimulation of inhibitory fibers or to be in reality a kind of shock. In Langendorff's and Nickell's [46] experiments this so-called shock did not continue following a unilateral section of the cervical cord; it was soon followed by bilateral breathing. Very early, Vupina [43] noticed that after unilateral section of the cervical cord, respiration came to a standstill only if the breathing had previously been weak. In the Brown-Séquard experiments under the same conditions respirations continued on the side of the lesion, but appeared somewhat weaker. Porter [47] later brought forward evidence to disprove Langendorff's work and also Wertheimer's [48] experiments; the latter was also a believer in a spinal respiratory center. Porter obtained a complete cessation of respiration on separating the bulb from the spinal cord (fig. 1) at the caudal end of the medulla, and concluded, therefore, that there is no respiratory center in the phrenic nuclei. Porter found it possible to make extensive lesions around the phrenic nucleus without arresting breathing. On making hemisections midway between the bulbar and phrenic nuclei he did not obtain arrest of respiration on either side. From the last two observations he concluded that respiratory impulses descending the lateral columns from the bulb can reach the phrenic nerve of the opposite side, and further that the impulses from the bulb can reach the phrenic nuclei of the opposite side at the level of the phrenic nuclei and nowhere else. Porter maintained that these crossed paths are always present and open to impulses, but that normally and under ordinary conditions probably only a few impulses pass. Deason and Robb,[49] repeating Porter's experiments, confirmed his results. Knoll [50] also noted that after a unilateral section of the medulla at the level of the calamus scriptorius the respirations on the hemisected side continued, although they were somewhat weaker. Porter would probably explain this weakness of the muscles of the hemisected side by saying (as his experiments have suggested) that most of the impulses passing down the intact side do not cross over, thus limiting the motion on the injured side as contrasted with the uninjured side.

46. Nickell, R.: Untersuchungen über das Centrum das reflectorischen Lidschlusses, Königsberg, R. Parbs, 1888.

47. Porter, W. T.: The Path of Respiratory Impulses from the Bulb to the Phrenic Nuclei, J. Physiol. **17**:455, 1894-1895.

48. Wertheimer, E.: Recherches expérimentales sur les centres respiratoires de la moelle épinière, J. de l'anat. et de la physiol. **22**:567, 1887.

49. Deason, J., and Robb, L. G.: On the Pathway of the Bulbar Respiratory Impulses in the Spinal Cord, Am. J. Physiol. **28**:57, 1911.

50. Knoll, P.: Beiträge zur Lehre von der Athmungsinnervation: Einfluss des centralen Nervensystems auf die Athmung, Sitzungsb. d. k. Akad. d. Wissensch. d. math.-naturw. Cl., Wien **92**:328, 1885.

Mislavski, Knoll,[51] Kron [42] and others obtained continuous respiratory movements after section below the bulb, but of an uncoordinated and arrhythmic character, with irregular thoracic and abdominal excursions. They believed that they were dealing with reflex respiratory convulsions; that, after all, the respiratory centers in the spinal cord had no sort of specialized significance, but like all other centers in the spinal cord could modify conditions only through a reflex mechanism.

It is, however, recognized that there are primary respiratory levels in the spinal cord. Gad [52] believed even that the inspiratory center in the medulla oblongata is subordinate to that in the spinal cord. The spinal cord is usually considered the center of the phrenic nerve and the nerves from the intercostal muscles. The phrenic center, which has the greater significance, lies in the region between the third and fourth to the sixth cervical segments. After section of the phrenic nerve, Kohnstamm [53] found degeneration of a group of cells in the anterior cells from the third to sixth segments.

As to the excitability of the spinal centers, the experiments of Schroff and Langendorff show that stimulation of these centers by carbonated blood in young animals under the influence of strychnine does not alter the rhythm of respiration. As has been suggested before by experiments on animals, it is probably only in young subjects that respiration continues after subbulbar section. A longitudinal cut in the upper half of the cervical cord divides the phrenic nuclei from one another. Under such conditions Nitschmann [54] observed that each side of the spinal cord called forth its own diaphragmatic movements.

As has been stated, a midline section of the cord does not destroy the respiratory movements, and each side functions rhythmically of its own accord. It has been observed that a section of the vagus causes a noticeable irregularity on the side of the cut nerve (Langendorff). Bechterew [31] maintained that impulses on the side of the cut vagus may be carried by the fifth nerve and that a bilateral reflex is thus obtained. Unilateral section below the medulla oblongata, however, produces a complete cessation of the respiratory movements on that side, evidently because the reflex has been destroyed. As was shown by Porter, it all depends on the point between the medulla and cervical cord at which the section is made.

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51. Knoll, P.: Beiträge zur Lehre von der Athmungs-Innervation, Sitzungsb. d. k. Akad. d. Wissensch. d. math.-naturw. Cl., Wien **97**:163, 1888.

52. Gad, J.: Natur und Lage des inspiratorischen Koordinationszentrums in der Medulla oblongata, Festschr. f. v. Leyden, Berlin, 1901, vol. 1.

53. Kohnstamm, O.: Zur Anatomie und Physiologie der Phrenicuskerne, Fortschr. d. Med. **16**:643, 1898.

54. Nitschmann, R.: Beitrag zur Kenntnis des Athmungscentrums, Arch. f. d. ges. Physiol., 1885, p. 558.

What may be concluded regarding the significance and importance of the respiratory nervous mechanism of the spinal cord? In most animals and under normal conditions the spinal cord cannot of itself support respiration for any length of time. This has been fairly conclusively proved by Porter [47] and others, although it is denied by a few. These centers act as subordinate levels for those found in the bulb (Bechterew). The significance of the spinal respiratory nuclei lies in the fact that they receive and relay impulses to a large number of muscles associated with respiration. It is known that the inspiratory movements of the thorax and diaphragm are not synchronous with one another, so that the costal expansion can continue while the diaphragm is relaxed. In other cases the intercostal inspiratory phase commences before the diaphragm begins to contract. Also, the respiratory movements of the nose and mouth begin ordinarily before those of the thorax. All this shows a certain independence of respiratory innervation of the different sets of respiratory muscles. And still these muscles must work in unison, which can result only from higher integration levels at some more cephalic place in the brain stem.

What is the significance of the bulbar respiratory mechanism? It is known that all parts of the cerebral hemispheres may be removed without respiration ceasing. Section below the facial nucleus causes a cessation of the respiratory facial movements. In cases of successive section of the cord from the thoracic nerves upward, the muscle groups that are supplied by the destroyed nerve roots will fall out. A section in the region of the fourth cervical nerve results in paralysis of the diaphragm; still higher, in paralysis of the neck muscles. Yet the respiratory movements of the face still continue in a definite rhythm. From this it follows that the bulbar respiratory mechanism still functions even though the peripheral neuromuscular system is damaged. With the respiratory impulses entering the medulla oblongata via the fifth, ninth and tenth cranial nerves, and in view of the fact that respiration continues following section of the pons and ceases when the bulb is divided from the cervical cord, one is forced to conclude that the medulla oblongata is one of the main levels of the brain stem for the integration of respiratory impulses.

Destruction of the nerve tissue at the levels of the cortex, midbrain, pons, medulla and spinal cord has resulted in a greater or lesser modification of respiration. Although no attempt has been made to review the literature, the recent work on the visceral connections of the diencephalon by Huber and Crosby [55] indicates that there is probably an integrating center for respiratory impulses in the region of the

55. Huber, G. C., and Crosby, E. C.: Somatic and Visceral Connections of the Diencephalon, Arch. Neurol. & Psychiat. **22**:187 (Aug.) 1929.

hypothalamus also. With such a distribution of the nervous respiratory mechanism there must obviously be certain fiber tracts that integrate these various levels. The pathways of the afferent and efferent impulses to and from the cortex are, no doubt, the sensory and motor voluntary pathways. The visceral connections to and from the diencephalon are not known with certainty, but are probably a series of connecting neurons extending from the hypothalamus to the midbrain. Since little is known concerning the respiratory nervous mechanism of the diencephalon, it is unwise to speculate further as to the paths by which impulses are carried caudad from this level. It is important, however, in order to interpret correctly the lesion found in the brain stem in the cases to be described, to know by what tracts afferent and efferent impulses coming to and from the several levels of the brain stem are conducted to the motor neurons giving rise to the final common path of the respiratory muscles.

Fiber Tracts Conducting Efferent Respiratory Impulses.—In the literature there are two conflicting opinions as to the location in the brain stem of fiber tracts conducting respiratory impulses: 1. The theory upheld by Bell, Schiff, Gad and Marinesco, Porter, Keller and others is that these respiratory fibers lie for the most part in the lateral columns. Schiff described them as lying close to the gray matter. Gad and Marinesco placed them in the anterior reticular formation of the spinal cord, dorsal to the anterior horn. Porter located them in the lateral part of the cervical cord. 2. The second theory is maintained by Brown-Séquard, Langendorff, Kohnstamm, Allen and others who, from work on animals, have demonstrated that section of the lateral columns is not sufficient to stop respiration, although breathing is slowed. These workers agree that the reticular formation of the medulla and spinal cord plays an important part in the integrative action of the respiratory impulses between the upper levels and the spinal cord.

As Allen's work is the most recent and probably the most complete in the light of earlier work, it will be described in more detail. First, however, the recent work of Papez[56] describing the course of the reticulospinal paths in the cat is worthy of consideration. He mentioned three main fiber tracts located in the reticular formation of the midbrain, pons and medulla and terminating around the anterior horn cells of the cervical cord: 1. The medial reticulospinal tract has two chief levels of origin (fig. 1), one from the large reticular cells of the pons and isthmus and another from the same large cellular elements of the upper medulla oblongata. He described the larger number of these fibers as passing down on the same side. This tract lies in the lateral part of the medial longitudinal bundle. At the level of the twelfth nucleus

56. Papez, J. W.: Reticulospinal Tracts in the Cat, J. Comp. Neurol. **41**:365, 1926.

the fibers spread out in the ventral part of the nucleus, lying medial, however, to the outgoing fibers of the hypoglossal nerve. They enter the cord lying ventromedial to the anterior horn. 2. The second group of fibers is the lateral reticulospinal tract (fig. 1). These fibers arise, for the most part, lateral to the masticatory nucleus and decussate just above Gudden's deep tegmental nucleus to reach the opposite inferior colliculus. In their course to the cord these fibers are described as lying medial to the masticatory nucleus, ventral to the facial genu and ventral to the lower trigeminal nucleus, entering the cord between the crossed pyramidal tract and the rubrospinal tract. 3. The ventral reticulospinal tract (fig. 1) takes its origin in the region of the upper pons, lateral to the reticular nucleus of Bechterew. It is also a crossed tract and can be traced dorsal to the trapezoid body and the medial lemniscus and lateral to the medial longitudinal bundle, and then along the dorsal accessory olive into the ventral funiculus of the cervical cord. Allen,[10] in his paper on the viscerobulbar pathways, confirmed the work of Papez in his description of the reticulospinal pathways terminating ventral and ventromedially to the anterior horn of the cervical cord. In an earlier paper on the respiratory pathways of the spinal cord, as has been mentioned, Allen[57] stated, and with good reason, that these reticulospinal tracts have an important place in the integrative action of the respiratory nervous pathways. Briefly, his experiments consisted of partial cross-sections of the cords of rabbits in the upper cervical region including lateral, dorsal, ventral and medial sections and hemisections. His conclusions from this set of experiments were, so far as they concern this paper, that following a lesion of the upper cervical cord, including a hemisection of the cord with severance of the medial division of the ventral column of the opposite side, complete section of both anterior columns or complete severance of the lateral columns, no impulses from the cerebrum and brain stem to the motor cells of the respiratory muscles were blocked. He obtained some modification of respiration in the more extensive lesions but never a complete cessation of the movements. However, when he made a lesion which severed both ventral columns and the medial half of each lateral column there was instant cessation of the respiratory movements. Allen therefore expressed the belief that both the lateral and ventral reticulospinal tracts are the main fibers in the spinal cord concerned with the conduction of respiratory impulses from the cephalic part of the brain stem to the respiratory nuclei of the spinal cord. It will be recalled that the lesion of the ventral columns and medial aspect of the lateral columns checks with the location of the ventral and lateral

57. Allen, W. F.: Visceral Bulbo-Spinal Pathways, J. Comp. Neurol. **42**:393, 1927.

reticulospinal tracts in the spinal cord given by Papez and also by Allen in his earlier paper (fig. 1).

The question that might arise is whether or not these reticulospinal tracts carry impulses all the way from the midbrain and pons to the cervical cord or, on the other hand, if the impulses might not be carried by the lateral columns at least as far down as the medulla, to be carried from this level by the reticular formation of the bulb to the cord. A recent paper by Keller indicated such a possibility. In his experiments on the cat to localize the polypnea center, he made several partial sections of the brain stem at the level of the inferior colliculus and pons as far caudad as the facial nucleus. He obtained marked interference with respiration when both lateral columns were severed. He also made lesions of the reticular formation (fig. 1, upper medulla) at these levels and obtained no marked change of the respiratory movements. His lesions in the reticular formation were very small, however, and destroyed only a small part of this region. His experiments strongly suggest that the lateral columns, at least at the level of the pons, conduct some of the respiratory impulses, but his results by no means rule out such a function of the reticular formation.

COMMENT

From the review of the literature with the accompanying schematic representation in figure 1, certain inferences and conclusions may be drawn and discussed:

1. The idea of a true respiratory nervous center should be discarded; I refer to the belief in the theory of a focal respiratory center located in one definite level of the brain stem. One has only to review the literature carefully and critically to be impressed with the folly of such a hypothesis. Flourens was one of the few workers on this problem who with certainty described a focal region in the brain stem which controlled breathing. Many more experimenters have placed the nervous respiratory mechanism in general at the levels of the reticular formation of the medulla (fig. 1); others include the reticular formation of the medulla, pons and midbrain. Still others are more inclusive in their localization, mentioning nuclear masses at the levels of the midbrain, pons, medulla, and cervical cord (Trevan, Langendorff, Bechterew, Coombs, Keller, Porter and others). It is clearly evident that if one takes a bird's eye view of the results of the experimental work on the nervous respiratory mechanism of animals, these results will show that respiratory movements may be directly modified by stimulation or destruction of nuclear masses and fiber tracts in the cerebrum, diencephalon, midbrain, pons, medulla oblongata and cervical cord. However, as is revealed by the anatomic facts and experimental results, the integration of respiratory impulses through afferent, efferent and

associative fiber tracts occurs at all levels of the central nervous system. The greatest level of coordination probably lies in the region of the reticular formation throughout the medulla oblongata. A given lesion at this level will therefore produce a more striking modification of the respiratory nervous integrative activities than a similar wound at other levels of the central nervous system.

The idea here expressed may seem contradictory, but one of the chief functions of the central nervous system is integration of nervous impulses. There are certain places in the brain where the integrative activities of special types of impulses are greatest; for example, impulses of vision in the occipital lobe, but also in the midbrain and thalamus; auditory impulses in the temporal lobe, but also in the pons and midbrain. Therefore, the greatest integrative activities of the respiratory impulses probably lie in the reticular formation of the medulla oblongata but also at other levels of the central nervous system (fig. 1).

The first of the two cases to be reported was studied and worked up thoroughly, both clinically and anatomically. From the clinical standpoint, case 2 is unsatisfactory, as the child was under observation in the hospital for only two days. However, anatomically, the lesion was so definitely localized to the reticular formation that the case can be reported with definite though limited value.

REPORT OF CASES

CASE 1.—A girl, aged 10, was referred to the New Haven Hospital on Aug. 13, 1927, with a condition diagnosed as poliomyelitis. Thirteen days previous to the date of admission, a swollen cervical lymph node was noted. There was no evidence of sore throat or cold at that time. On August 10, three days before admission, the patient felt nauseated and refused to eat. That evening she vomited and had a temperature of 102 F. Although she retained some food, vomiting continued throughout the next day. On August 11, two days before admission, she complained of difficulty in swallowing and of pain in the back of the neck. Late the next morning, her voice became hoarse, and by night she was unable to talk. On several occasions, when she attempted to swallow, fluid passed through the nose.

The family history was irrelevant.

Examination.—On admission, the child appeared well developed and nourished and not acutely ill. She was completely aphonic and unable to swallow. The ocular movements were normal and the pupils reacted to light and in accommodation. There was a questionable left facial paralysis. Hearing was unimpaired. There was no discharge from the external auditory canal and the ear-drums were normal. The mouth was full of saliva. The soft palate was immobile with the uvula in the midline. No exudate was noted in the region of the posterior pharynx. The observations on the chest were not unusual except for a rough systolic murmur heard over the precardiac region with a fine palpable thrill. Respiration was normal. The abdomen and genitalia were normal. There was no apparent weakness of the extremities, and all movements were performed with

ease. The tendon reflexes were absent on the left and were elicited with difficulty on the right. The abdominal reflexes were active and equal. The Kernig and Babinski reflexes could not be elicited. There was no stiffness of the neck.

Examination of the blood showed: red cells, 4,800,000; hemoglobin, 85 per cent; white cells, 25,000; polymorphonuclears, 85 per cent; lymphocytes, 9 per cent, and large lymphocytes and transitionals, 9 per cent. In the urine there was a heavy trace of albumin, the reaction for acetone was 4 plus, no sugar was present and from 8 to 10 leukocytes were found in each high power field. The spinal fluid was negative for acetone, the pressure was "normal" and there were 21 white blood cells per cubic millimeter, 5 per cent of these being polymorphonuclears. The Pandy test gave a 1 plus reaction.

Course.—The child was given dextrose by hypodermoclysis and rectal administration during the entire period of hospitalization, because she was unable to swallow. On August 15, two days after admission, respirations suddenly became rapid, ranging between 30 and 50 per minute. It was debated at this time whether or not the tachypnea was due to a beginning pneumonia from aspirated material or to a beginning respiratory paralysis. There were no physical signs of pneumonia. The margins of the ribs on both sides were noted to be elevated and flattened, indicating paralysis of the diaphragm. Continuous administration of oxygen was started.

On the following day, an examination by the attending neurologist disclosed the following: The patient's voice had a soft nasal quality. Attempts to swallow caused choking and considerable discomfort. There was no movement of the larynx on attempts to carry out the act of deglutition. On attempted phonation the uvula became slightly elevated and pulled to the left. The third, fourth, fifth, seventh and twelfth cranial nerves showed no evidence of involvement. There was no indication of paralysis of the limbs. The deep reflexes were feeble or absent, as were also the superficial reflexes. Respirations at the moment seemed to be chiefly abdominal, with little movement of the thoracic wall. The lower intercostal spaces were sunken. The fundi were not remarkable.

On August 17, there was some improvement in the paralyzed muscles. The voice and ability to swallow had returned somewhat. On the following day, however, the patient's temperature rose to 41 C. (105.8 F.), and both the deep and the superficial reflexes completely disappeared. Suddenly, on the morning of August 22, eight days after admission and following a restless night, the child's head became retracted. Later in the afternoon of the same day, respirations ceased for several seconds. The returning respirations were ineffective, becoming rapid and shallow, and the resulting cyanosis required the administration of oxygen for the second time. An examination, five hours later, still disclosed no signs of pneumonia. In the afternoon of the same day, respiration practically ceased and artificial respiration was instituted. The pulse slowly became weaker and more rapid, and the child died eight hours later. The immediate cause of death was thought to be a bulbar form of poliomyelitis with particular involvement of the respiratory mechanism; starvation, acidosis and a possible bronchopneumonia were also thought to be contributory.

Necropsy.—The report of the observations will be limited to the central nervous system. Gross examination of the brain and brain stem did not reveal any pathologic changes. The brain was fixed in 10 per cent commercial formaldehyde three hours after death.

Microscopic Observations: Twelve hundred serial sections through the caudal end of the pons, entire medulla and the upper part of the cervical cord were

prepared and stained by the iron hematoxylin method. Only the lesions of critical levels will be described.

A study of these serial sections disclosed definite pathologic changes throughout. The more advanced pathologic process, such as necrosis, was seen in the lower pons and upper medulla, together with congestion and cellular infiltration. The changes throughout were for the most part limited to the gray matter.

A section through the pons at the level of the trapezoid body showed no areas of degeneration. A high power lens did not reveal perivascular infiltration or necrosis. No abnormal changes were apparent in the cells making up the nuclear masses at this level. Somewhat more caudal to this section a lesion was noted at the inferior pole of the superior olivary nucleus. It was situated in the reticular substance on the left, midway between the motor nucleus of the sixth nerve and the median raphe, dorsal to the superior olivary nucleus. At this point the nerve cells and both longitudinal and transverse fibers of the reticular formation had

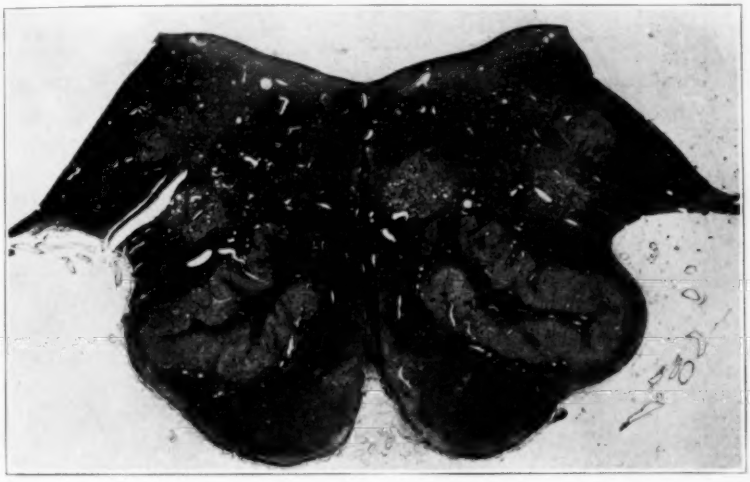

Fig. 2 (case 1).—Section through the upper third of the medulla. Three zones of necrosis, two on the right and one on the left; × 7.

been destroyed. At the junction of the pons and medulla another lesion made its appearance on the right side of the median raphe in the lateral part of the reticular formation. The lesion on the left side was still present at this level, and was in the same relative position as that just described on the right side.

Figure 2 shows the lesions at a level through the upper third of the inferior olive. Three distinct lesions are seen clearly in the photomicrograph. The lesion on the left side is a direct continuation of the one already described. The medial lesion on the right lies just lateral to the medial longitudinal fasciculus and dorsomedial to the inferior olive. The lateral lesion is larger and lies midway between the inferior olive and the restiform body in the direct pathway of the lateral reticulospinal tract and olivocerebellar fibers. Both involve the reticular formation. Although the lateral one also lies in line with the somatic motor nucleus of the seventh, ninth and tenth cranial nerves, this level is about midway between the nucleus ambiguus and the motor nucleus of the seventh.

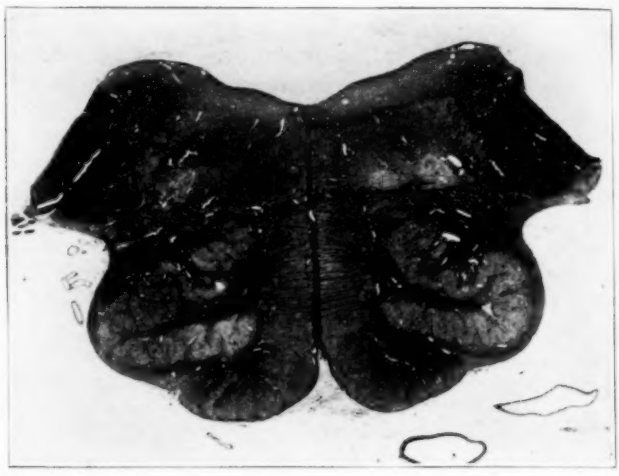

Fig. 3 (case 1).—Section through the middle third of the medulla. Two lesions of the right lie well within the reticular substance; the lesion on the left side lies on the border line of this area; × 7.

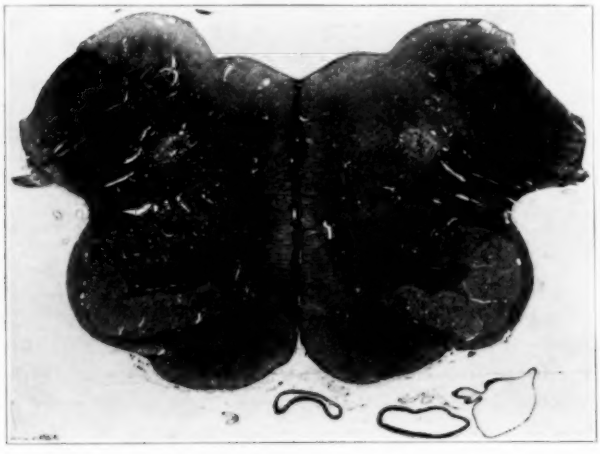

Fig. 4 (case 1).—Section through the lower third of the medulla. One lesion on each side involves the lateral part of both reticular regions; × 7.

In figure 3, which is slightly more caudal, the two lesions on the right lie closer together, the medial one being smaller and in a more lateral position. This lesion lies in the pathway of the reticulospinal tract described by Papez, while the more lateral lesion lies in the pathway of the ventral reticulospinal tract. The two lateral lesions on each side have involved not only the reticular formation, but the cephalic portion of the nucleus ambiguus. Fiber bundles passing through these areas appear indistinct and in some instances are entirely lacking. The longitudinal fibers of the reticular formation are also indistinct.

Figure 4 is taken through the level of the lower third of the inferior olive. It is to be noted that only one lesion remains on the right. The bilateral lesions noticed at this level involved almost symmetrical areas in the substance of the reticular formation. Careful microscopic observations of the serial sections in this region showed extensive damage of the cells in the nucleus ambiguus. Figure 5, through the most caudal end of the medulla, does not reveal a necrotic area on either side.

From the stain used in the serial sections it is not possible to describe the specific changes that took place in the zones of necrosis (fig. 6). The vessels both within and surrounding these areas were intensely congested. There was marked cellular perivascular infiltration of small and large mononuclear cells. Other cells with pale vesicular spherical nuclei were noted but they do not show up well in the photomicrograph (fig. 6). They resembled the so-called "Gitterzellen" or phagocytic microglia.

Many of the nerve cells in the necrotic areas were missing, and those lying near the border were swollen. The changes occurring in the ones that remained were not as marked as one might expect. The cytoplasm in all of them took the stain poorly. Most of the nuclei showed no changes. Some of them were eccentrically placed in the cell body, and in occasional instances the nuclear membrane was missing. Many of the cells undergoing necrosis were surrounded by several phagocyte-like cells, while an occasional nerve cell was actually in the process of being taken up by these phagocytic cells. The blood vessels of the nuclear masses in the lower pons and medulla oblongata were greatly congested. Many focal areas of small round cell infiltration were seen, particularly in the dorsal nucleus of the vagus, in the nucleus of the twelfth nerve and in the reticular formation. Sections through the caudal end of the medulla and the upper half of the pyramidal decussation also disclosed congested blood vessels throughout the gray matter.

The anterior horns showed the most marked changes in the cord. In both horns there was a congestion of the blood vessels. Perivascular infiltration was present only in the left anterior horn. Here the larger vessels were surrounded by a wall of cells, several layers thick. The cells were decreased in number as compared with those in the right anterior horn in which no damage to the ganglion cells was evident. In the left, however, not only was there a decrease in the number, but most of those remaining showed obvious pathologic changes. The Nissl bodies were missing in many. In others the nucleus was eccentrically placed and the cell membrane missing. Occasionally fragments of a nucleus were seen surrounded by a clear hollow space. Many of the remaining cells were swollen and their nuclei were enlarged and vesicular. No changes were present in the cells of the posterior horns, although the blood vessels were congested.

Summary.—The important regions involved were the reticular formation of the lower pons and the upper two thirds of the medulla, the nuclei ambigui and the left anterior horn of the cervical cord.

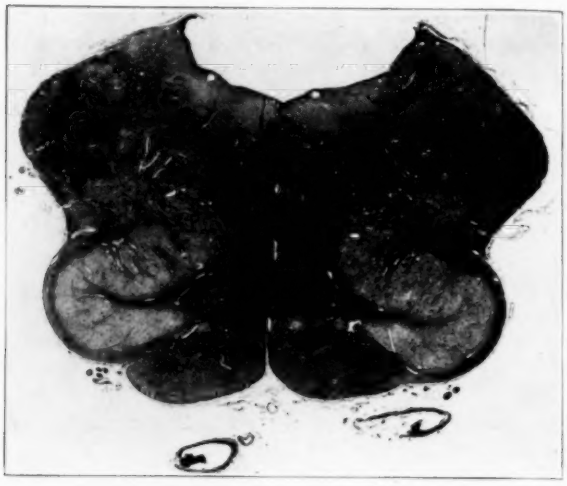

Fig. 5 (case 1).—Section through the caudal end of the medulla. No lesions are present at this level; × 7.

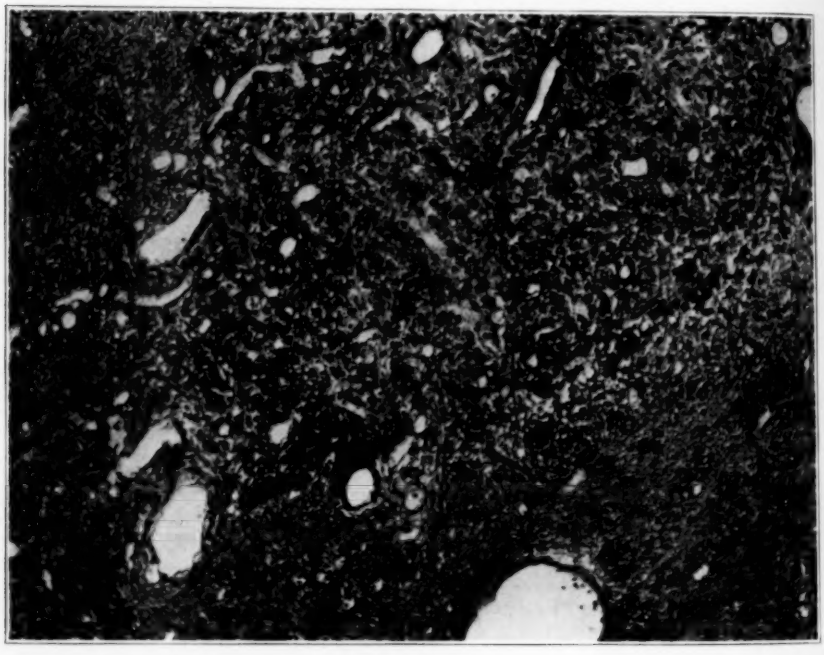

Fig. 6 (case 1).—High power photograph of the necrotic area in the medulla showing perivascular infiltration of mononuclear cells, destruction of nerve tissue in the reticular formation and large numbers of phagocytic microglia cells; × 125.

CASE 2.—*History.*—A boy, aged 18 months, on June 21, 1930, developed a temperature of 102 F. and a cough, and became irritable and weak. There were also occasional twitching of the face and irregular movements of the eyes. He made no attempt to sit up or walk. Two days later, a local physician found the child stuporous and paralyzed and sent him to the hospital with the diagnosis of infantile paralysis and pneumonia.

Examination.—On admission (June 27, 1930), the patient's temperature was 39.8 C. (103.6 F.), and his respirations were rapid, shallow, irregular and noisy. He was completely flaccid and remained in the position in which he was placed. There was a complete left facial paralysis, and nystagmus with occasional strabismus were also noted. Purulent material was present in the throat, but the

Fig. 7 (case 2).—Section through the lower pons. There is a large focus of necrosis to the right and a smaller focus to the left of the midline involving the region of the reticular substance of the pons; × 8.

mucous membrane was not particularly congested. The gag reflex was present. The neck was slightly rigid. The percussion note was resonant over the entire right side of the chest and over the lower lobe of the left lung, but was impaired over the upper left lobe. Fine crepitant and moist râles were heard over the dull region. There was complete flaccid paralysis of all four extremities and of the anterior abdominal wall. All reflexes of the extremities and abdomen were absent. The Kernig sign was also absent. No further complications appeared until the second day in the hospital when the child unexpectedly gave a sudden gasp and respirations ceased.

Examination of the blood showed a normal red cell count with a white cell count of 18,200 and 76 per cent polymorphonuclear cells. The spinal fluid was under normal pressure, with 15 cells per cubic millimeter and a 1 plus Pandy test.

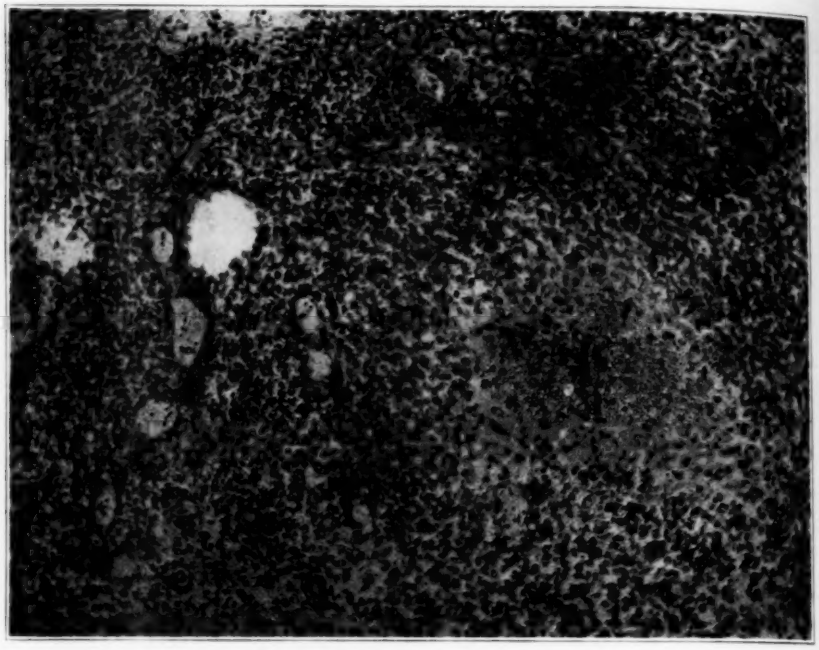

Fig. 8 (case 2).—High power photograph of the large necrotic zone to the right of the median raphe of the medulla. A large area of hemorrhage is present in the right and throughout the photomicrograph are seen large numbers of phagocytic microglia cells; × 100.

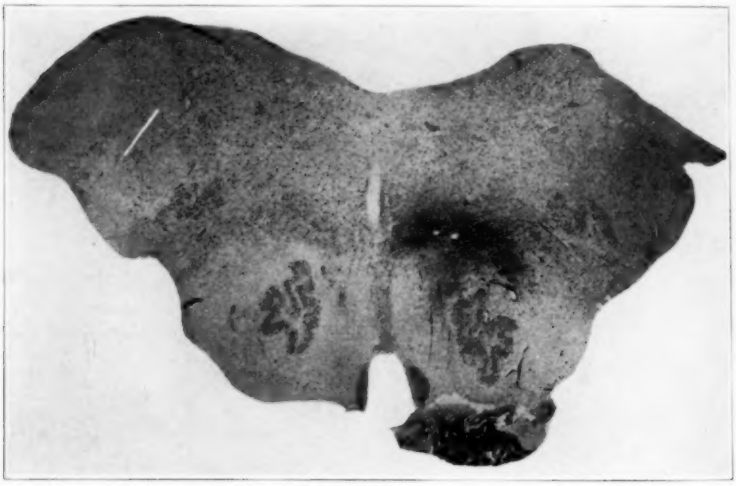

Fig. 9 (case 2).—Section through the upper part of the medulla. There is a large lesion in the reticular substance on the right with a beginning involvement of a similar region to the left of the midline; × 8.

Diagnosis.—The final diagnosis was: (1) poliomyelitis, acute bulbar; (2) pneumonia, lobar.

Necropsy.—The studies of the thoracic and abdominal viscera were limited to the lungs; complete consolidation of the upper left lobe was found, with a few scattered small areas of consolidation in the remaining lobes of both lungs.

The pathologic changes in the central nervous system, except for small foci of microglial proliferation in the left cornu ammonis, were limited to the midbrain, pons, medulla and cord. Grossly there was found at the lower end of the pons and in the upper two thirds of the medulla a circumscribed lesion of necrosis and hemorrhage involving particularly the reticular formation on the right. A smaller, though distinct, lesion was also present in the same location on the left side. No disturbance of the architecture was seen in the lower third of the medulla or the cervical cord.

Sections were taken from the hemispheres and seven different levels of the midbrain, pons, medulla and cervical cord. They were prepared by the Nissl technic.

A large ischemic area in the midbrain showing no cellular detail was present on the right, involving the reticular formation and the superior cerebellar peduncle. This lesion crossed the midline to involve to a less extent the same structures on the left. In the pons was seen the necrotic focus that had been observed grossly. There was complete destruction of the nerve cells and fibers of the reticular formation on the right. On the left the involvement was less extensive but in a similar location (fig. 7). A small focus was also present in the left facial nucleus. Small foci of glial rosettes were present in other parts of the midbrain. The region in the reticular formation showed extensive necrosis of and hemorrhage into the nerve tissue. Throughout the necrotic area there were large numbers of phagocytic microglia (fig. 8). The destruction of the reticular substance extended caudad into the reticular substance of the upper medulla and was most marked on the right (fig. 9). A section through the middle of the medulla showed no involvement on the left. The lesion on the right was still present, though much smaller. No changes were seen, however, in the lower third of the medulla. In the anterior horns of the cervical cord there was perivascular infiltration with lymphocytes and polymorphonuclear cells. The necrosis, hemorrhage and microglial reaction noted in the medulla and pons were lacking. Several anterior horn cells that appeared normal microscopically were present, but the number was definitely decreased bilaterally. An occasional pathologic form of cell was observed.

Summary.—There was almost complete destruction of the reticular formation of the midbrain, pons and upper two thirds of the medulla on the right, with partial destruction of the same region on the left. In the cervical cord there was perivascular infiltration with absence of some of the anterior horn cells.

The point of particular interest in these two cases is the correlation between the respiratory failure and the pathologic changes found in the nervous system. It is important, however, to rule out other causes, aside from a neuropathologic process, in accounting for the respiratory failure. Respiratory failure is a common sign in pneumonia. The attack of rapid respiration in case 1 soon after admission to the hospital was followed by no signs of pneumonia. There was, however, a striking immobility of the wall of the chest together with other signs of

bulbar involvement. Just before death, evidences of pneumonia were carefully watched for, but none appeared. There was anatomic evidence of not far advanced pneumonia in the right lower lobe. It should be emphasized that, though the reflexes were weak or absent in case 1 (this varied from time to time), there was no actual paralysis of the extremities, as all movements could be performed with ease. There was, on the other hand, definite paralysis of the pharyngeal muscles.

In case 2 the pneumonia probably played a more predominant part in the child's illness. The malady was present early in the illness and anatomically was more extensive than in the former case. However, the child died unexpectedly and with a sudden gasp. The death of a child with pneumonia is usually not unexpected, nor does the child's life terminate as it did in this case. It is well known clinically that respiratory failure is one of the most common causes of death in poliomyelitis of the bulbar type, these two cases being striking examples. Anatomic study in both cases revealed a marked involvement of the bulbar levels of the brain stem with minor involvement of the cervical cord. In case 1, clinical evidence of bulbar involvement was maximal, while in case 2 signs of involvement of the cord were probably more prominent. Anatomically, however, bulbar involvement was the outstanding picture in both cases.

SUMMARY

From the review of the literature it has been shown that the respiratory neural mechanism is an integrative mechanism, and that this integration takes place in part at several levels of the central nervous system. Experimental work points toward the reticular formation of the brain stem as one of the primary regions for the integration of respiratory impulses. Two integrative levels are involved in the lesions found in the cases reported: (1) the upper cervical cord with congestion, round cell infiltration and partial destruction of the anterior horn cells; (2) the reticular formation in which were found bilateral focal areas of necrosis, limited almost entirely to this portion of the brain stem. Destruction of the motor cells of the left anterior horns, as has been suggested, can account for a partial paralysis of the diaphragm. The paralysis of the intercostal muscles is undoubtedly accounted for by involvement of the thoracic cord by similar changes.

However, these changes do not account for a complete cessation of respiration. If the lesions shown in the bulbar part of the brain stem (figs. 2 to 7) are compared with similar regions in figure 1, it will be noted that these necrotic areas lie at the levels and in the region on which most emphasis has been placed by experimental workers as the main integrative level for respiratory impulses. It has been shown that the patients in the cases here reported died primarily of respiratory

failure, which, with the anatomic observations, not only substantiates much experimentation with animals on this problem, but, more important, further favors the hypothesis that the reticular formation is a level for the integration of respiratory impulses.

CONCLUSIONS

1. The central respiratory neural mechanism is not localized at any one level of the brain stem, but extends throughout the central nervous system.

2. A summary of the literature reveals that one of the main integrative levels for respiratory impulses has been considered to lie in the reticular formation.

3. The opinion is here expressed that, on the basis of the clinical and anatomic observations and the experimental work herein described, the respiratory failure in the cases reported was due primarily to the lesions in the reticular formation of the brain stem and possibly to the changes in the anterior horn of the upper cervical cord.

THE GRASPING REFLEX IN THE NEW-BORN MONKEY *

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In 1891, Robinson [1] found that a new-born human infant is able to support its own weight when holding on to a horizontal rod. He tested sixty infants, and found that all except two could hang for at least ten seconds, and one infant hung for two minutes and thirty-five seconds. Robinson believed that this ability is due to the presence of a primitive grasping response seen in monkeys and apes, by means of which the new-born monkeys hold on to the hair on the under surface of the mother's body. It occurred to me that it would be of interest to know more about the reflex in new-born monkeys, particularly as to its strength in comparison with the reflex of the new-born human infant and its persistence after birth.

Hitherto there have been no opportunities for making such observations. It is only in recent times that it has been possible to breed monkeys successfully in laboratories, and new-born monkeys still are not plentiful. I was fortunate in having the opportunity of obtaining records of the grasping reflex from birth or within the first weeks of life to the time of the disappearance of the reflex in five monkeys born in the *Rhesus* colony of the department of embryology of the Carnegie Institution. Dr. Carl Hartman cooperated with me in this work.

METHODS

It was necessary to develop a simple technic for measuring the reflex in monkeys. I first tried hanging the monkey from two horizontal bars, but found that this was not feasible because the monkey invariably let go with one hand and changed from one hand to the other. This made it impossible to obtain a consistent measure of the strength of the reflex. It was then decided to measure the reflex of one hand at a time. For this purpose the two legs and one of the arms were tied together, leaving free only the hand to be tested (fig. 1). This worked very well. The monkey was held by the back of the neck, and the palmar surface of the extended hand was brought into contact with the horizontal rod. This contact is sufficient to elicit the grasping response. Immediately after the animal has obtained a firm grasp on the bar, the experimenter releases the animal so that it hangs freely, unsupported. The length of time it hangs gives a measure of the strength of the reflex.

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* Submitted for publication, Feb. 19, 1931.

* From the Phipps Psychiatric Clinic of the Johns Hopkins Hospital.

1. Robinson, Louis: Nineteenth Cent. **30**:831 (July-Dec.) 1891.

Fig. 1.—Photograph showing the grasp response of a new-born monkey and the method of tying the free arm and the two legs.

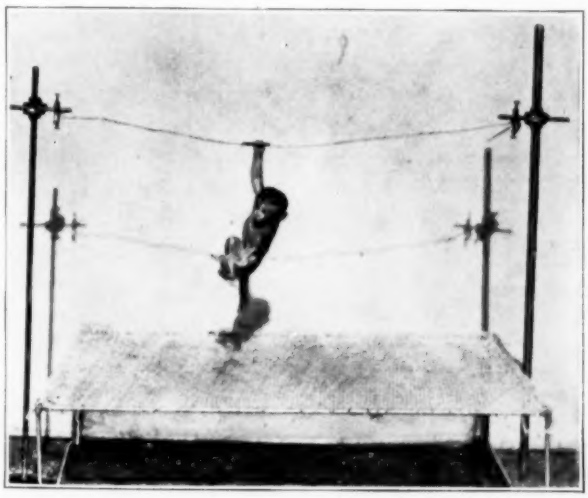

Fig. 2.—Photograph showing a new-born monkey hanging from a bar over a net, in which it is caught when it falls.

The apparatus necessary for this experiment is a bar and a net to catch the animal when it falls (fig. 2). A piece of iron wire, one-eighth inch (0.3 cm.) thick and covered with rubber tubing, was used for the horizontal bar. It was clamped firmly at both ends to upright metal stands. A one-half inch (1.27 cm.) mesh cord fishing net was suspended on an iron frame 39 inches (98.5 cm.) square, supported on legs 1 foot (30.48 cm.) from the floor. The bar was placed about 2 feet (69.96 cm.) above the net.

Records of the grasping reflex were made about four times a week up to the time the reflex disappeared. One measurement was made each time on the right and left hands. In order to eliminate any difference in the strength of the reflex on the two sides, which might arise from fatigue, alternate hands were used each time for the first record.

The monkeys remained with their mothers throughout the course of the experiment. They were taken away just long enough each time to permit the records to be taken. Thus they were able to grow up under normal and healthful conditions.

RESULTS

The five new-born monkeys tested showed a grasping response that was markedly stronger than that of the new-born human infant. One animal hung for thirty-three minutes by one hand; two minutes and thirty-five seconds was the longest record for the human infant hanging by both hands.

The reflex showed marked variations from day to day, and also a wide range of variation in different individuals, as may be seen in the graphs of the reflex of the five animals shown in figures 3, 4, 5, 6 and 7.

The monkey whose record is shown in figure 3 hung for three minutes and thirty seconds with its right hand and for one minute and twenty seconds with its left hand on the first day after birth. The reflex gradually decreased in strength from then to the tenth day. After that it showed a steady increase until the time when the longest record for hanging was made, on the twenty-sixth day. On that day it hung for seventeen minutes and ten seconds with the left hand and for nine minutes and ten seconds with the right hand. From then on it showed almost a precipitous decrease to a level of less than one minute. The reflex disappeared completely on the forty-first day.

The next monkey, whose record is given in figure 4, hung for slightly less than a minute from both the right and the left hands on the first day the records were taken, that is, when the animal was 7 days old. From then on, the reflex increased in strength until it reached a peak of eleven minutes on the fifteenth and sixteenth days. It decreased rapidly after that to a temporary low level on the twenty-third day, and then increased steadily to a second maximum on the fifty-first day. After a second sudden drop it disappeared completely on the seventy-sixth day.

A somewhat similar record, shown in figure 5, was obtained from another monkey. It also shows two maxima, one at the sixth and

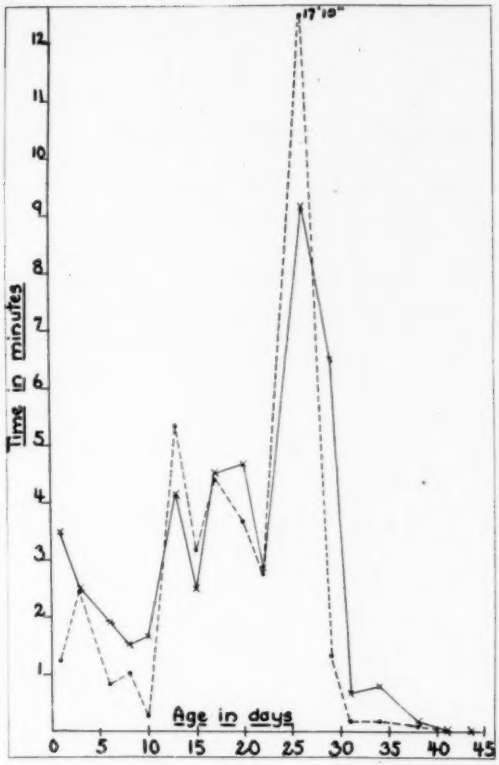

Fig. 3.—Graph showing the strength of the grasp reflex of the right (continuous line) and the left (broken line) hands of a monkey (V) from the age of 1 to 41 days. The highest record was reached on the twenty-sixth day.

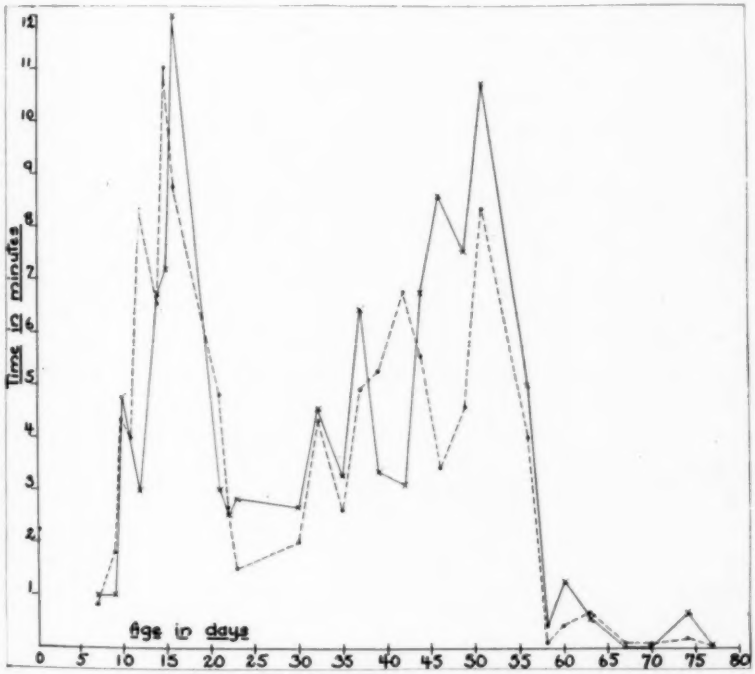

Fig. 4.—Graph of the grasp reflex of a monkey (66[1]), showing two maxima, one at the fifteenth and one at the fifty-first day.

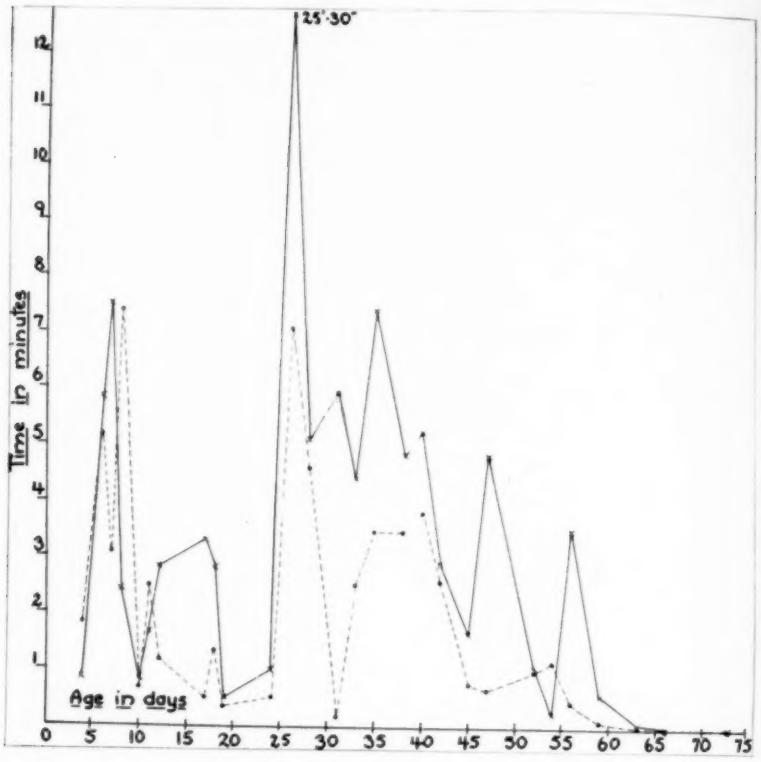

Fig. 5.—Graph of the grasp reflex of a monkey (65[1]), also showing two maxima, one at the sixth and one at the twenty-sixth day.

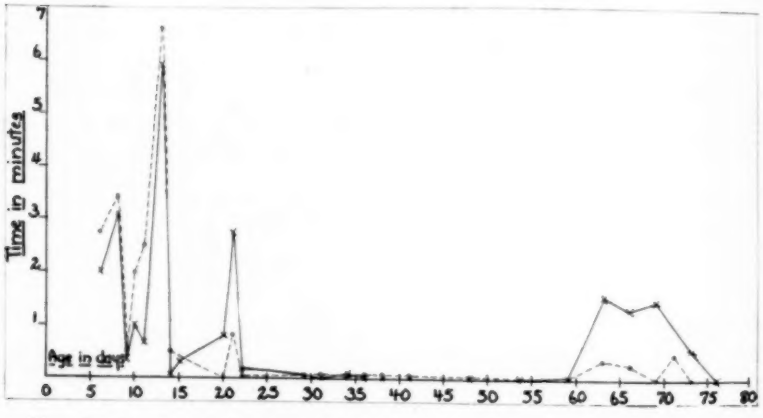

Fig. 6.—Graph of the grasp reflex of a monkey (114[1]) in which the reflex disappeared after the forty-first day and returned again for a short period on the sixty-third day.

seventh days and one at the twenty-sixth day. The reflex disappeared at the sixty-sixth day, that is, at almost the same time as in the previous animals.

In the next animal the reflex was strongest on the thirteenth day (fig. 6). It was very weak after that and disappeared temporarily on the forty-first day. It returned again on the sixty-third day and remained until the seventy-sixth day.

The record in figure 7 shows, in contrast to the previous records, a much greater consistency. The reflex increased steadily until the maxi-

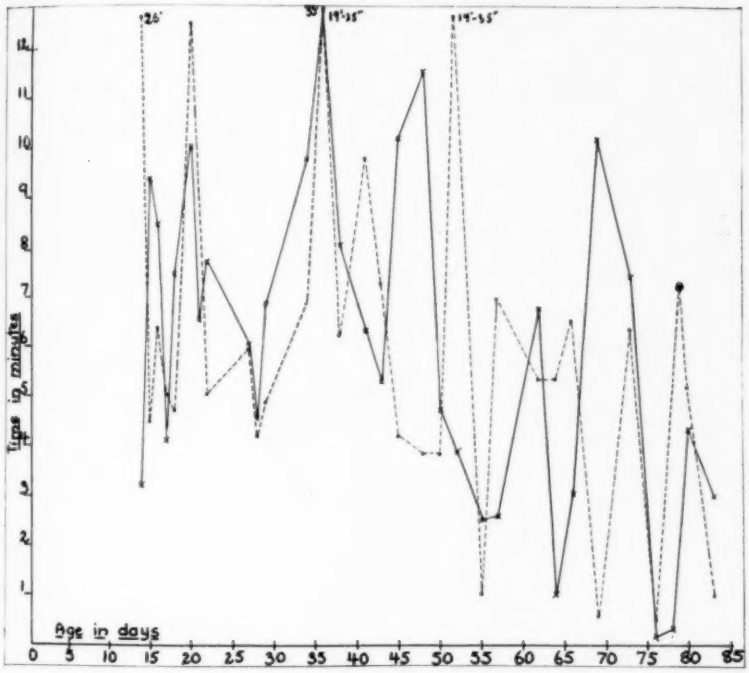

Fig. 7.—Graph of the grasp reflex of a monkey (U), showing a gradual increase up to the maximum on the thirty-sixth day and a gradual decrease from then on. The reflex was still present on the eighty-third day, when the experiment was discontinued for unavoidable reasons.

mum was reached on the thirty-sixth day, and then decreased again very steadily. It was weak but present on the eighty-third day, when the measurement was interrupted for unavoidable reasons. The reflex seemed to be much stronger in this animal than in any of the others, and it persisted for a much longer period. The curves showed a consistent steady increase to the maximum and a steady decrease thereafter. There were unaccountable fluctuations from day to day.

In all of the animals the reflex was equally strong in the right and left hands.

SUMMARY

1. The grasping reflex is much stronger in the new-born monkey than in the new-born human infant. The longest record obtained by Robinson in human infants hanging from both hands was two minutes and thirty-five seconds, whereas one of the monkeys hung for over thirty-three minutes by one hand alone. There is no doubt that, as the monkey can hold on with only one hand for thirty minutes, it can hold on for hours with both hands and feet.

2. The reflex is not strongest at birth but reaches its maximum from fifteen to thirty-eight days later.

3. The reflex disappeared in four animals at the ages of 41, 65, 71 and 71 days, and was still present at 83 days in the fifth animal.

4. The reflex was equally strong in the two hands.

5. There were marked and unaccountable fluctuations in the strength of the reflex from day to day.

6. The reappearance of the reflex in adult monkeys under pathologic conditions, produced by experimental lesions of the brain and the administration of different drugs, will be discussed in a later paper.

NEURONS OF THE SENSORY TYPE IN THE VENTRAL ROOTS OF MAN AND OF OTHER MAMMALS*

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Recently, I reported [1] that the spinal accessory nerves of the cat and the monkey are not purely motor, as is generally supposed. A few nerve cells of the sensory type were observed scattered along their course, and even small ganglia were found occasionally.[2] Aberrant collections of neurons are known to occur in man [3] also. That those observed in the cat are associated with fibers in the nerve seems to be indicated by the fact that they undergo chromatolysis when the eleventh nerve is cut at its place of entrance into the sternocleidomastoid muscle. These observations raised the question of the possible presence of similar neurons in the motor roots of the spinal nerves. It was realized that a search might not yield any, because the ventral spinal roots are not homologous to the accessory; nevertheless, a survey of the literature revealed that other observers have reported such elements in various animals, including man.

In 1878, Freud [4] examined the spinal cord and nerve roots of *Petromyzon*, and reported that, in the caudal region, the ventral roots contain small but distinct ganglion cells near the place where the roots divide into the dorsal and ventral branches. Not more than one cell was observed on any; they were usually bipolar elements, similar to those of the sensory ganglia. Another observation on lower vertebrates is that of Onodi,[5] who recorded the presence of nerve cells in the

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1. Windle, W. F.: The Sensory Components of the Spinal Accessory Nerve, J. Comp. Neurol. **53**:1, 1931.

2. Van der Sprenkel observed small ganglia on the rootlets of the accessory nerve in the hedgehog embryo (Ariëns Kappers, C. U.: Die vergleichende Anatomie des Nervensystems der Wirbeltiere, Haarlem, de Erven F. Bohn, 1920, vol. 2, p. 524).

3. Weigner, K.: Beziehungen des Nervus accessorius zu den proximalen Spinalnerven, Anat. Hefte **17**:549, 1901. Fahmy, N.: A Note on the Intracranial and Extracranial Parts of the Ninth, Tenth and Eleventh Nerves, J. Anat. **61**:298, 1927.

4. Freud, S.: Ueber Spinalganglien und Rückenmark des Petromyzon, Sitzungsb. d. k. Akad. d. Wissenschaft, Wien **78**:87, 1879.

5. Onodi, A. D.: Ueber die Ganglienzellengruppen der hinteren und vorderen Nervenwürzeln, Centralbl. f. d. med. Wissenschaft, Berlin **23**:275 and 291, 1885.

ventral roots of the dogfish, *Scyllium*. A distinct ganglion containing a number of round cells was found on one of these.

A number of brief and little known references to these elements in mammals have been made. In 1881, Schäfer [6] called attention to the fact that, just as isolated ganglion cells are sometimes found in the portions of the dorsal roots proximal to the ganglia, so can they also be observed in the ventral roots of the cat. He found them most numerous in the lower thoracic and lumbar regions, but did not mention the number of specimens examined. Schäfer declared that they are not present in the dog, rabbit, mouse and man. In 1893, Tanzi [7] confirmed the observations on the cat, adding that they occur at all ages, and, what is more important, that the frequency of their appearance does not seem to decrease with age in extra-uterine life. The cells were found to be exactly like those of the spinal ganglia, corresponding mainly to the medium-sized ones. They were found singly or in groups of two or three, often arranged with their long axes parallel to that of the root. Tanzi did not find any within the spinal cord, but reported that they were present at various places both proximal and distal to the part of the roots that lies adjacent to the dorsal ganglia. In the following year, Kölliker [8] found nerve cells in the remaining portion of the ventral roots of the cat. He was of the opinion that they were either sympathetic or sensory.

After sectioning the ventral roots of the cat and the monkey, Sherrington [9] found a few degenerated myelin sheaths in the portion central to the cut and a few undegenerated fibers in the peripheral segment. He believed some to be recurrent fibers from the sensory ganglia, and others to be axons of occasional cells that he found in the ventral roots. The cells lay in close relationship to the bundles of from 5 to 40 recurrent fibers and were sometimes arranged in rows of 4 or 5. They resembled the smaller cells of the spinal ganglia, but Sherrington was inclined to believe that some were sympathetic cells.

Three references to the existence of nerve cells in the ventral roots of man have been made. Hoche [10] reported some in the emerging rootlets just outside, as well as within, the cord in the lumbar and sacral regions. They varied between 30 and 80 microns in diameter;

6. Schäfer, E. A.: Note on the Occurrence of Ganglion Cells in the Anterior Roots of the Cat's Spinal Nerves, Proc. Roy. Soc., London **31**:348, 1881.

7. Tanzi, E.: Sulla presenza di cellule gangliari nelle radici spinali anteriori del gatto, Riv. sper. di freniat. **19**:373, 1893.

8. Kölliker, A.: Ueber das Vorkommen von Nervenzellen in den vordernen Würzeln der Rückenmarksnerven der Katze, Neurol. Centralbl. **13**:744, 1894.

9. Sherrington, C. S.: On the Anatomical Constitution of Nerves of Skeletal Muscles; With Remarks on Recurrent Fibres in the Ventral Spinal Nerve-Root, J. Physiol. **17**:211, 1894.

10. Hoche, A.: Ueber die Ganglienzellen der vorderen Würzeln im menschlichen Rückenmarke, Arch. f. Psychiat. **23**:586, 1892.

no processes could be seen in the sections, and, in general, they resembled sensory neurons. In teased preparations, he was able to observe a nuclear capsule and a single process which, in some cases, divided in a T-like bifurcation. Zachariades [11] was unable to find cells in the position in which Hoche found them, but he did observe a good many farther distad on the sacral roots. He reported that they occurred singly or in groups, and bore a close resemblance to the medium-sized cells of the spinal ganglia. He discredited the idea that they may be sympathetic by stating that, in teased preparations of roots fixed in osmic acid, he was able to observe a single process that was well myelinated and received a neurilemma sheath from the capsule of the cell.

Only recently, Piolti [12] found cells of the sensory type in the ventral roots of the cat, guinea-pig, dog and man. Very few occurred in the dog and none in the squirrel, but in the other animals a considerable number was reported. He stained the thoracic and lumbar ventral roots of two new-born kittens by the Nissl method, and found 45 and 414 cells, respectively. They occurred in all parts of the roots and were round or ovoid, and some were oriented with their long axes parallel to the motor fibers. He reported that the tigroid substance was finely scattered in the cytoplasm, and held the cells to be identical with the obscure cells of Lugaro [13] (that is, the small ones of the spinal ganglia). In man, they were seen best in the lumbar roots. There also they resembled, in every way, the small cells of the dorsal ganglia. In Cajal preparations he found them to be unipolar, their axons having a tendency to form glomeruli as do those of the cells of the sensory ganglia.

From this brief review it may be seen that sensory neurons are not unknown in the ventral roots of a number of different animals, including man. The evidence points to the presence there of cells that in all ways resemble the small and medium-sized ones of the dorsal ganglia. That they occur in all ventral roots has not been indicated; no extensive study has been made to determine whether or not they are ever present in significant numbers in man. Whether their processes bifurcate and whether the resulting branches pass through the ventral roots to the cord and peripheral nerves is not known. The results of most of the attempts to prove physiologically that conduction of sensory impulses takes place over the ventral roots appear to be negative or, at least, open to question.

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11. Zachariades, P. A.: Sur l'existence de cellules ganglionnaires dans les racines antérieures sacrées de l'homme, Paris, G. Steinheil, 1896.

12. Piolti, M. M.: Sur la présence de cellules sensitives dans les racines antérieures de la moelle épinière, Rev. neurol. **1**:1146, 1930.

13. Lugaro, E.: Sulla patologia delle cellule dei gangli sensitive, Riv. di pat. nerv., 1900-1903, vols. 5, 6, 7 and 8; abstr. by Orr, D.: Rev. neurol. & psychiat. **2**:228, 1904.

The classic experiments of Claude Bernard [14] on recurrent sensibility do not indicate that impulses pass into the spinal cord over the ventral roots. In dogs, this observer found that stimulation of the peripheral portion of the ventral roots, after they had been sectioned, gave rise to pain responses if the dorsal roots were intact, but that stimulation of the central segments of the cut roots did not elicit responses. Lehmann [15] believed that he had observed the persistence of visceral sensibility after section of a dorsal root. His work has been criticized by Meyer,[16] however, who presented good evidence that in cats careful, complete sections, which were extensive enough to include all of the nerves to a given extremity, resulted in complete anesthesia of the limb affected. The experiments of Shaw [17] on rabbits have been cited in support of Lehmann's work, but they are not convincing because of the high percentage of failures and because of the inadequate criteria used to determine the persistence of sensation. Davis and Pollock [18] recently reported the complete loss of sensation in seven cats in which the dorsal roots from the fourth cervical to the sixth thoracic had been cut on one side. They subsequently decerebrated the animals, and showed that no reflexes could be elicited in the leg on the deafferented side either by homolateral or by contralateral stimulation.

On the other hand, clinical evidence has been offered to show that some sort of sensation may persist after section of a series of dorsal roots. The most impressive experiment, to which, however, other interpretations may be given, is that of Foerster and his colleagues,[19] who, in resecting the sympathetic trunk from the sixth to the tenth thoracic vertebra, unwittingly ligated the ninth thoracic nerve near its exit through the intervertebral foramen. The pain resulting from this was not relieved after a second operation had been performed, during

14. Bernard, Claude: Leçons sur la physiologie et la pathologie du système nerveux, Paris, J. B. Baillière et fils, 1858.

15. Lehmann, W.: Ueber die sensiblen Fasern in den vorderen Würzeln und ihre Beziehung zur Sensibilität der visceralen Organe, Ztschr. f. d. ges. exper. Med. **12**:331, 1921; Ueber die sensiblen Fasern der vorderen Würzeln, Klin. Wchnschr. **3**:1895, 1924.

16. Meyer, A. W.: Verlaufen sensiblen Fasern in den vorderen Würzeln? Zentralbl. f. Chir. **48**:1790, 1921; Ueber die fraglichen sensiblen Fasern der vorderen Würzeln, Deutsche Ztschr. f. Chir. **199**:38, 1926.

17. Shaw, R. C.: A Study of Intractable Pain Relative to Rhizotomy and Spinal Section, Brit. J. Surg. **11**:648, 1924.

18. Davis, L., and Pollock, L. J.: The Peripheral Pathway for Painful Sensations, Arch. Neurol. & Psychiat. **24**:883 (Nov.) 1930.

19. Foerster, O.; Altenburger, H., and Kroll, F. W.: Ueber die Beziehungen des vegetativen Nervensystems zur Sensibilität, Ztschr. f. d. ges. Neurol. u. Psychiat. **121**:139, 1929.

which from the seventh to the eleventh thoracic dorsal roots were cut. These authors concluded that the only pathway that the painful impulses could have taken was over the ventral roots. Most of the clinical data on this subject have been adequately reviewed by Wartenberg [20] and will not be given at this time. Although the ventral roots have been assumed to conduct sensation antidromically by those who hold that the Bell-Magendie law is not infallible, it is surprising that little or no attention has been paid to the literature concerning the presence of sensory cells within them. That most of the articles, mentioned briefly here, have been ignored is understandable, however, because many are obscure and difficult to obtain, and are seldom quoted by anatomists and physiologists. The purpose of the present article is to call attention to these observations, and to record new ones of a similar nature.

TABLE 1.—*Number of Cells in the Anterior Roots of a Six Months Old Human Fetus*

Root	Left	Right	Comment	Root	Left	Right	Comment	Root	Left	Right	Comment
C_1	0	0	.....	T_3	3	0	.....	L_1	27	21	.....
C_2	1	0	.....	T_4	5	0	.....	L_2	3	20	.....
C_3	0	0	.....	T_5	4	0	.....	L_3	3	9	.....
C_4	0	0	.....	T_6	1	1	.....	L_4	0	1	.....
C_5	1	44	All scattered	T_7	2	4	.....	L_5	0	0	.....
C_6	1	8	.....	T_8	1	6	.....	S_1	0	2	.....
C_7	0	3	.....	T_9	1	5	.....	S_2			
C_8	0	1	.....	T_{10}	3	3	.....	S_3			
T_1	32	0	Ganglion	T_{11}	5	12	.....	S_4	124	53	81 cells in ganglion
T_2	4	0	.....	T_{12}	12	13	.....	S_5			
								Co			

EXPERIMENTAL OBSERVATIONS

Human Material.—An aborted fetus of about the sixth month was obtained. It had been placed in a diluted solution of formaldehyde, U. S. P. (1:10), soon after delivery, but, when it came to the laboratory two days later, it was found that fixation of the structures beneath the skin had not taken place. Consequently the skin was removed, the cranium and vertebral canal were opened, and the specimen was placed in fresh formaldehyde. A week later, all of the ventral nerve roots were dissected out and prepared for histologic examination, care being taken to obtain all of each root from its attachment to the cord to a point opposite the spinal ganglion. They were placed in individual vials, stained in bulk in a 0.04 per cent solution of safranin to which was added an acetate buffer (p_H 4), sectioned serially by the paraffin method (10 microns thick), and examined.

Many of them did not contain nerve cells, but frequently one or more cells of the sensory type were located along the course of the roots, and in several instances definite small ganglia were present; these usually consisted of 5 or 6 cells of various sizes, but one contained 32, and another, 81 cells. The data obtained from this study are presented in table 1. The position of the cells does not seem to be constant, for they may occur anywhere along the course of the roots. In most cases, the cells were actually in the roots among the motor fibers, but occasionally

20. Wartenberg, R.: Klinische Studien zur Frage der Geltung des Bell-Magendieschen Gesetzes, Ztschr. f. d. ges. Neurol. u. Psychiat. **113**:518, 1928.

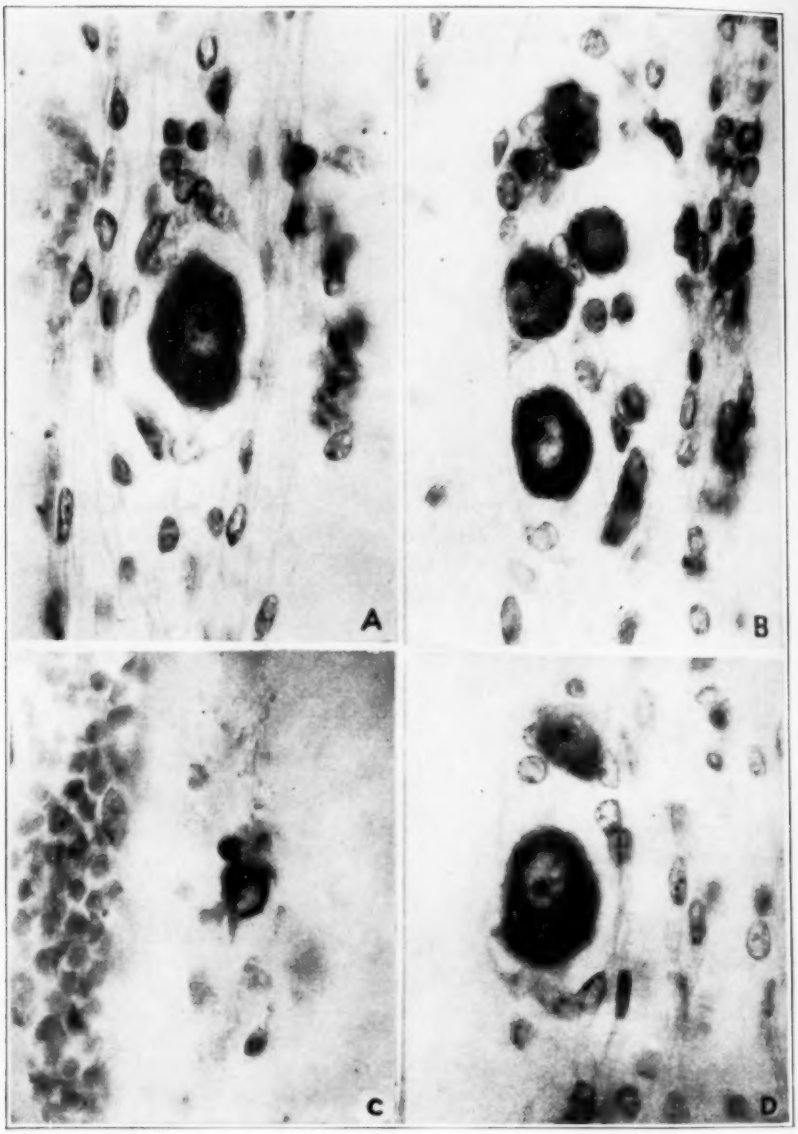

Fig. 1.—Photomicrographs of cells of the sensory type in the ventral roots of a 6 month old human fetus. *A* shows one of the largest cells lying in a small fascicle of motor fibers near their exit from the cord; the axon hillock of the cell may be seen. In *B* portions of 6 large and medium-sized cells may be observed. This is a section through one of the occasional ganglia of the ventral roots located near the surface of one of the larger fascicles of motor fibers. *C* illustrates one of the smallest neurons. *D* was taken from a section through a small cluster of cells. Safranin stain; × 650.

one was found at the surface of the root or even in the connective tissue about it. The latter position was characteristic of many of those observed in the cervical region.

Such elements were round or ovoid and quite like the ones found in the dorsal roots ganglia. None was larger than 28 microns in diameter; the smallest were only 9 microns but the majority measured between 17 and 21 microns. The cells of the ganglia of the dorsal roots of the same fetus were found to have about the same variation in size, but a few were larger than 30 microns. Therefore, the cells of the ventral roots corresponded to the small, medium-sized and even the moderately large ones of the dorsal roots. In Nissl-granule pattern, the cells of the ventral roots were similar to those of the dorsal roots; some had a well stained ground substance, with fine, evenly scattered granules, while others, especially the larger ones, presented a clearer cytoplasm containing coarser granules. The nuclei and nucleoli were typical of nerve cells; some double nucleoli were noted. In no case could more than one process be seen arising from a cell of the ventral

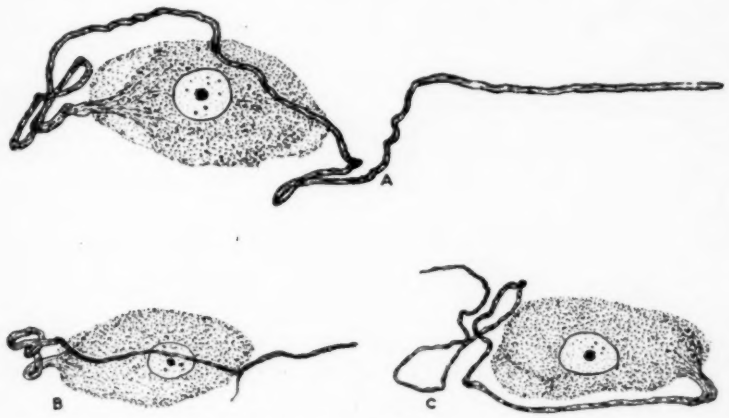

Fig. 2.—Camera lucida tracings of three cells of the sensory type in the lower lumbar ventral roots of the cat. In each case, the course of the axon was carefully determined under the binocular, monobjective microscope equipped with stereoscopic ocular caps. Tracings of the cell and its process were then made from the several adjacent sections in which they occurred. These were superimposed to make the finished illustration; in this way, the course of the coiled axon could be illustrated. The presence of glomeruli is characteristic of primary sensory neurons. A branch of the axon is shown in *B;* this may be the axonal bifurcation, but it is probably a small collateral. The long axes of the cells are parallel to the fibers of the ventral roots, which are not illustrated. Pyridine-silver stain, according to the method of Ranson; × 750.

root, and in a number of specimens single distinct axons with axon hillocks were observed (fig. 1*A*). Of course, the method used does not differentiate nerve fibers, and, to compensate for its failure to do so, some of the slides were restained by the alcoholic silver nitrate method of Davenport.[21] However, this method does not produce good pictures of embryonic and fetal nerve fibers, and little was gained

21. Davenport, H. A.: Staining Nerve Fibers in Mounted Sections with Alcoholic Silver Nitrate Solution, Arch. Neurol. & Psychiat. **24**:690 (Oct.) 1930.

by the process. By the Davenport technic, the cell bodies stained in the manner typical of nerve cells, and could be toned with gold to advantage. No data were obtained on the question of the distribution of cell processes in the human material; neither glomeruli nor bifurcations of axons were seen.

The Dog and the Cat.—Ventral roots of these animals were prepared by the pyridine-silver method of Ranson in the hope of being able to study the cell processes to better advantage. In the dog no cells were found, but several were observed in the lower lumbar roots of the cat. They were unipolar, encapsulated cells of sensory type, and the axons, when traced through several sections, could be seen to coil near the cell bodies. These coils, or glomeruli, are illustrated in figure 2. In one case, what appeared to be a bifurcation of the axon was observed (fig. 2 *B*). The axons of these cells measured 2 microns or less in diameter, and were either of the small myelinated or the unmyelinated variety. The fiber arising from the cell shown in figure 2 *B* joined a distinct group of small fibers among which several unmyelinated ones could be seen.

TABLE 2.—*Normal Fibers in Degenerated Ventral Roots of the Dog and Cat*

Animal	Sectioned Ventral Roots	Degeneration, Number of Days	Normal Fibers	Cells
Dog 1	Left S_1	7	None	None
	Left S_2	7	From 12 to 18 fibers of medium and small size in a single compact fascicle	None
Dog 2	Left S_1	9	None	None
	Left S_2	9	None	None
	Right S_1	9	2 small fibers	None
	Right S_2	9	None	None
Cat 1	Left L_7	12	4 small fibers	1
	Left S_1	12	2 small fibers	2
	Left S_2	12	3 small fibers	None
	Left S_3	12	None	None

In order to determine whether there are as many myelinated, centripetal fibers in the ventral roots as there are cells of sensory type, the following experiments were performed. In two dogs and one cat a few of the lumbar and sacral dorsal and ventral roots were sectioned as near the cord as possible, and time was allowed for degeneration of the myelin sheaths. The roots were then carefully removed, fixed and stained in osmic acid, sectioned longitudinally in series (5 to 10 microns thick), and examined for normal sheaths and nerve cells. The data are presented in table 2. Although, in the dog, no nerve cells were found in the few roots examined, 2 normal myelinated axons in one case, and a bundle of from 12 to 18 in another, were seen. Likewise, in the ventral roots of the cat, the number of cells observed was less than the number of normal fibers. Although 3 cells were present, no myelinated fibers could be seen arising from them, and it may be assumed that their axons were unmyelinated, at least close to the cell bodies. Judging from these experiments, it seems probable that there are more sensory nerve fibers than cells located in the ventral roots.

COMMENT

This study confirms the presence of nerve cells in the ventral roots of man, and indicates strongly that, if they function at all, they are sensory. That they are not sympathetic efferent neurons is shown by

their morphology: The Nissl pattern is typical of sensory cells; they are unipolar, encapsulated elements, and, at least in the cat, their axons form glomeruli. The variation in size corresponds to that of ganglion cells of the dorsal root. The question naturally arises as to whether the large number found in the 6 month old fetus might not diminish greatly in the adult. The observation of Tanzi [7] that they occur as frequently in the adult cat as in young kittens indicates that one might also expect to find considerable numbers of them in the adult human being. Apparently no one has examined all of the ventral roots of man, but from the studies of Hoche,[10] Zachariades [11] and Piolti,[12] it is known that sensory cells are present in some of them, and there is no reason to believe that some roots in the adult may not contain considerable numbers of them. Although the present study was made on a fetus, it is evident from the accompanying photomicrographs that the cells possess most of the adult characteristics. They are much smaller than mature nerve cells, but this is partly due to the fact that the tissue was not well preserved and considerable shrinkage, which is clearly shown in the illustrations, took place. For this reason their true size could not be determined.

Little evidence has been presented that sheds light on the distribution of the axons of these cells. In the ventral roots of the dog and cat, the presence of occasional medium and small myelinated nerve fibers that did not degenerate after the roots were cut near the cord has been described in the present study, as well as in that of Sherrington [9] (on the cat and monkey). Although none was observed to arise from a cell in any of the roots, it may be assumed that they do come from cell bodies located elsewhere peripherally rather than in the spinal cord, because both dorsal and ventral roots were sectioned. It is probable that some sensory fibers present in the ventral roots arise in the dorsal ganglia, and the total number of these is, of course, not indicated by counting the cells of the ventral roots. There is a possibility that some of the neurons under consideration send their processes into the spinal cord by way of the ventral roots and to the peripheral sense organs by way of the spinal nerves. This arrangement might explain some of the persistence of pain after rhizotomy that has been reported clinically. However, the assumption that many or, in fact, any of the fibers course peripherad is not warranted; the lack of unquestionable physiologic evidence of conduction centrad over the ventral roots throws doubt on this theory. It is more probable that the undegenerated fibers observed are those for recurrent sensibility,[14] and it may be that the nerve cells of the ventral roots belong in this category too. If this is true, their processes do not course very far peripherad, but turn back toward the ganglia of the dorsal roots and pass over these roots to the spinal cord. Further experimentation is needed to determine whether or not this is actually the case.

There is a possibility, on the other hand, that the sensory neurons of the ventral roots have more than one function. It may be true that some subserve recurrent sensibility to the meninges, while others may course peripherad and thus be capable of conducting impulses from the periphery after the dorsal roots have been sectioned. It might even be suggested that many of them lack function under normal conditions, but it is unlikely that a ganglion containing 32 or more cells is entirely functionless. Still others may supply the blood vessels of the nerve roots and spinal cord. A number of the cells observed in the present study were located close to blood vessels in the ventral roots, and in one pyridine-silver preparation the axon of one followed the course of a vessel for a short distance. Nerve fibers that resemble those of sensory type have been observed on the blood vessels of the spinal cord by Clark;[22] their cells of origin are unknown. Some of the ventral root cells observed in the present study were located in the very fine rootlets near the spinal cord, and Hoche[16] reported some even within the cord. It is not unlikely that these may be concerned with the innervation of the blood vessels as well as the meninges of the cord.

Although it is possible that the neurons of sensory type of the ventral roots may be responsible for a number of functions, it would be unwise to ascribe any physiologic activities to them on the basis of the scanty evidence that is available at the present time. It is probable that future studies will show that one or another function deserves consideration.

CONCLUSIONS

In a 6 month old human fetus, nerve cells were found in most of the ventral roots. They occurred singly, in small clusters or even in little ganglia containing as many as 81 cells. The morphology of the cells indicated that they were sensory: their variation in size, the Nissl-granule pattern and the presence of nucleated capsules typical of the sensory neurons of the dorsal ganglia. They were unipolar, and, at least in the cat, their axons formed glomeruli as they left the cell bodies.

In some cases, there were more centripetal fibers than nerve cells in the ventral roots, and this adds to the probability that sensory fibers may occur frequently enough to be of functional significance. The axonal distribution of the sensory neurons located in the ventral roots is not known. Several possibilities have been considered, but no conclusions as to their function have been reached.

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22. Clark, S. L.: Innervation of the Blood Vessels of the Medulla and Spinal Cord, J. Comp. Neurol. **48**:247, 1929.

ANATOMIC VARIATIONS OF THE CRANIAL VENOUS SINUSES

THEIR RELATION TO THE EFFECT OF JUGULAR COMPRESSION IN LUMBAR MANOMETRIC TESTS *

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When one compresses the internal jugular veins, the obstruction to the outflow of the cranial circulation is reflected in a rise of the cerebrospinal fluid pressure. This principle is the basis of the Queckenstedt test,[1] in which the rise of spinal fluid pressure, noted by means of a manometer attached to the lumbar puncture needle, denotes the patency, or absence of block, in the subarachnoid space. In 1925, Tobey and Ayer [2] modified this test for the detection of thrombosis of the transverse or lateral sinus. Briefly, their test depends on the fact that if the transverse sinus, forming the chief intracranial tributary of the internal jugular vein, is occluded, it will not act as an outflow for the cerebral circulation. Hence, unilateral compression of the vein of the affected side will not produce increased obstruction to the circulation, and consequently there will not be a rise in the spinal fluid pressure. The vein on the unaffected side has had to take over the entire outflow, and therefore its compression will cause a rise equal to that of bilateral compression in a normal person. This test is now being used not only for the diagnosis of thrombotic occlusion of the lateral sinus but for occlusion from any cause, such as a tumor of the cerebellopontile angle.[3]

It should be noted that lumbar puncture in patients with subtentorial tumors is not without danger, as sudden death from respiratory failure occasionally occurs. When the spinal fluid pressure has been lowered by lumbar puncture, the increased pressure within the cranium jams the medulla oblongata down into the foramen magnum and death results. Fremont-Smith and Hodgson have performed combined lumbar and ventricular puncture to obviate this danger (The Human Cerebro-Spinal Fluid, New York, Paul B. Hoeber, Inc., 1926, p. 172).

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* Submitted for publication, Feb. 10, 1931.

* From the Anatomic Laboratory of Tufts College Medical School, and the Examiner's Office.

* Read at a meeting of the Boston Pathologic Society, Feb. 20, 1931.

1. Queckenstedt: Zur Diagnose der Rückenmarkskompression, Deutsche Ztschr. f. Nervenh. **55**:325, 1916.

2. Tobey, G. L., and Ayer, J. B.: Dynamic Studies in Lateral Sinus Thrombosis, Arch. Otolaryng. **2**:50 (July) 1925.

3. Gardner, W. J.: The Tobey-Queckenstedt Test in the Localizations of Tumors of the Cerebellopontile Angle, Arch. Neurol. & Psychiat. **20**:585 (Sept.) 1928.

In determining spinal fluid pressure, there are many possibilities of error.[4] 1. The position of the patient is important. He should lie as nearly horizontal as possible, so that gravity will not affect the pressure of the column of fluid between the skull and the lumbar region. The head should be in very slight extension or midposition, and should not be turned to one side or the other; otherwise one or both of the internal jugular veins may be partly compressed.

2. The patient must be comfortable and not apprehensive. Coughing, grunting, sobbing, holding the breath or muscular tension due to emotional excitement greatly raise the venous pressure,[5] and will increase the cerebrospinal pressure through the veins of either the spine or the skull.

3. The force of compression should be adequate and equal on the two sides. The vein is a thin-walled vessel, and if the fingers are properly pushed backward in the region of the anterior border of the sternocleidomastoid muscle, much force will not be required. Too much force can easily be applied. Such pressure may become uncomfortable. The resulting apprehension may cause irregular respiratory movements and a consequent rise of pressure. This rise may occur in an actual case of occluded transverse sinus and may make one believe that the sinus is patent.[6]

4. In unilateral compression, the time of compression should be equal on the two sides. One may choose a time of ten seconds or more, but should adhere to this time on both sides because the rise in pressure is certainly not fullest at the first touch of the finger. "In fact the promptness of response to jugular compression and the promptness with which the pressure returns to the original level, after jugular release, are more important than the actual height to which the pressure reaches (provided an adequate rise of at least 50 to 100 mm. from unilateral compression or at least 100 to 200 mm. from bilateral jugular compression, takes place)" (Fremont-Smith).

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4. Tobey and Ayer (footnote 2). Stookey, B., and Klenke, D.: A Study of the Spinal Fluid in the Differential Diagnosis of Diseases of the Spinal Cord, Arch. Neurol. & Psychiat. **20**:84 (July) 1928.

5. Eyster, J. A. E.: Clinical Aspects of Venous Pressure, New York, The Macmillan Company, 1929.

6. Unilateral carotid compression will probably not influence the cerebrospinal pressure. Vagal stimulation, on the other hand, may well produce a rise in pressure. This may occur through inhibition of respiration; or as Forbes and Wolff (Cerebral Circulation, Vasomotor Control of Cerebral Vessels, Arch. Neurol. & Psychiat. **19**:1057 [June] 1928) have shown, stimulation of the vagus produces a dilatation of the pial arteries with a concomitant rise in cerebrospinal fluid pressure.

Even in the presence of expert attention to these details of technic, a certain number of patients with presumably normal sinuses and veins show variations to compression of each vein separately. I have examined about 150 consecutive records at the neurologic service of the Boston City Hospital containing full data on the manometrics of the spinal fluid. Excluding all cases in which there was any suspicion of subarachnoid block, or occlusion or compression of the lateral sinus, one third of the cases showed variation in pressure on separate compression of the two sides to an extent of sufficient magnitude to seem significant. In one case, compression of one side gave no rise, while compression of the other gave a prompt and full rise and fall. This was repeated several times and confirmed by several observers. In these cases the greater rise occurred almost three times as often on the right side as on the left.

Other observers have noted similar conditions. Tobey and Ayer stated that in normal persons there may be a difference in the effect of compression on the two sides, but that a difference of over 50 mm. of water is unusual. They mentioned the possibility that this normal variation is due to a variation in the size of the sinus, but quoted H. P. Mosher as stating that there is no demonstrable difference in the sinuses on the two sides. Claude, Lamache and Aubry [7] recorded variations in pressure of from 1 to 2 cm. of water as common, and stated that this variation is explained by a difference in venous caliber that may exist on the two sides.

Such variations, based on some normal factor, may occasionally prove a stumbling block in diagnosis. W. J. Gardner of the Cleveland Clinic, writing in 1928 on the use of the jugular compression test in the diagnosis of tumors of the cerebellopontile angle,[3] reported five suspected cases. Four of these showed signs of partial occlusion of the lateral sinus which was proved at operation. In the fifth, however (case 2):

> The patient was suspected of having a tumor of the cerebellopontile angle on the right side. [On spinal puncture . . .] the initial pressure was 12 cm. of water. Responses on straining and coughing were normal. . . . With bilateral compression of the jugular vein, the pressure rose from 12.5 to 21 cm. of water, and promptly fell on release of the pressure. On compression of the left jugular vein there was a rise of only 2 cm. in ten seconds. On compression of the right jugular vein there was a rise in pressure of 4 cm. of water.

Typical signs of multiple sclerosis subsequently developed in this patient.[8] It is evident that reliance on the diagnostic significance of the

7. Claude, H.; Lamache, H., and Aubry, M.: Compression des veines du cou et tension céphalorachidienne, Compt. rend. Soc. de biol. **96**:261 (Feb. 4) 1927.

8. Gardner, W. J., personal communication to the author.

manometric observations would have caused much confusion. In his communication to me, Dr. Gardner adds:

> It has subsequently been my experience, that in most normal individuals the response on left jugular compression is not as marked as on right jugular compression. This I have always considered as due to the fact that the left jugular vein does not carry as much blood as the right.

REPORT OF CASE

I believe that the key to the situation does indeed lie in the comparative size of the transverse sinuses. The following case of Dr. Frank Fremont-Smith illustrates this to a remarkable extent.

History.—A white man, aged 33, entered the Boston City Hospital on Nov. 10, 1930, with symptoms of vomiting, failing vision, weakness of the left side and ringing in the left ear. Transient diplopia was present. A staggering gait with a tendency to fall to the left was noted. Deafness of the left ear and numbness of the left side of the face, neck and head were recent symptoms. Neurologic examination showed: nystagmus in all components; left nerve deafness; a high palate on the right; protrusion of the tongue to the right. There was dysmetria of both arms, and staggering gait to the left.

Spinal Fluid Dynamics.—On November 19, a lumbar puncture was performed by Dr. Fremont-Smith. His report read: "The patient was lying with the head slightly below the level of the lumbar spine; he was cooperative and relaxed. The initial pressure was 110 (mm. of water). Respiratory oscillations were not seen; the pulse oscillations were from 1 to 2 mm. When the manometer was tilted to one side, the fluid ran up and back freely, but came to rest at a pressure of 140. On deep inspiration, there was a fall to 130, and then a gradual fall to 120 mm. Bilateral jugular compression gave a prompt rise to 240 and a prompt fall to 130. When repeated, there was a prompt rise to 320, and a prompt fall to 110. The pulse oscillations were now from 2 to 3 mm., and respiratory oscillations were visible for from 5 to 6 mm. Jugular compression on the right (with the patient lying on the right side) gave a prompt rise to 220 and a prompt fall to 110. Jugular compression on the left, with greater pressure, gave a slow rise to 190 and a rather slow fall. When jugular compression was repeated several times on the left, both the rise and the fall were slower than on the right. On the right, only the slightest touch was needed to produce a prompt rise. On the left, deep and uncomfortable pressure was needed. After the removal of from 1 to 2 cc. of fluid, with the head raised slightly to the level of the lumbar spine, the pressure was 105. After a total of 4 cc. had been removed, the pressure was 60. The dynamics were repeated by a different observer with the same results, i. e., a prompt rise and fall with bilateral jugular compression or with jugular compression on the right, but a slow rise and rather slow fall after jugular compression on the left.

Impression.—"The intracranial pressure was normal. There is partial obstruction in the left lateral sinus or the internal jugular vein. The clinical picture, with deafness, tinnitus, nystagmus, etc., suggests the possibility of a tumor of the cerebellopontile angle, and the results of the unilateral jugular compression test would seem to confirm this diagnosis. The normal intracranial pressure of 140 mm., however, does not seem consistent with such a diagnosis, and certain of the clinical features suggests a more diffuse lesion, probably involving the pons."

Operation.—On December 2, a suboccipital exploration was performed by Dr. Tracy J. Putnam. "A tumor of the pons was revealed which had not caused increased intracranial pressure. It was of course impossible to remove. A simple suboccipital decompression was made. The patient recovered well from the operation, but his condition was not improved and he died on the next day."

Autopsy.—Only a small bit of tumor, 0.4 cm. in diameter, projected from between the cerebellar tonsils posterior to the brain stem. The pons was widened, particularly on the left, and the projecting tumor was found to be part of a tumor about 3 by 3.5 cm., infiltrating the left side of the pons, brachium conjuctivum, tonsils of the cerebellum and upper medulla. Microscopic examination showed a medulloblastoma.

Comment.—No part of the projecting bit of tumor, or of the brain infiltrated by it, was nearer than 1 cm. to the left transverse sinus. The possibility of pressure being transferred to the more yielding, posterior part of the sinus by way of the cerebellum seemed improbable in view of

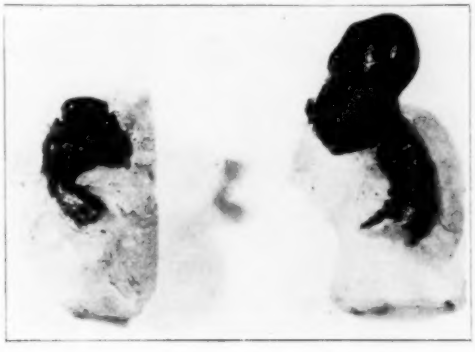

Fig. 1.—Photograph of the casts of the terminal portions of left and right transverse sinuses and jugular bulbs from the case described (actual size).

the normal pressure. It seemed certain that the tumor was in no way responsible for the diminished blood flow in the left transverse sinus.

Examination of the sinuses proper, however, served to elucidate the cause for the diminished response on the left side. Figure 1 shows a paraffin cast of the terminal (sigmoid) portions of the transverse sinuses and the jugular bulbs in this case. A glance will serve to show that the right sinus and bulb is tremendously larger than the left. The left sinus was 0.4 cm. wide and 0.2 cm. deep, while the right measured 0.6 by 0.5 cm. The bulb was correspondingly large. This observation, I believe, completely explains the result of the jugular compression test. Since the left side carried much less blood than the right, compression on the left had a correspondingly diminished effect on the cranial venous outflow and therefore a diminished effect on the rise of the cerebrospinal fluid pressure.

ANATOMIC STUDY

In order to determine the frequency of such variations, a study of the venous sinuses of about seventy skulls was carried out. Of these I have listed fifty consecutive specimens in this report. Roughly, one half

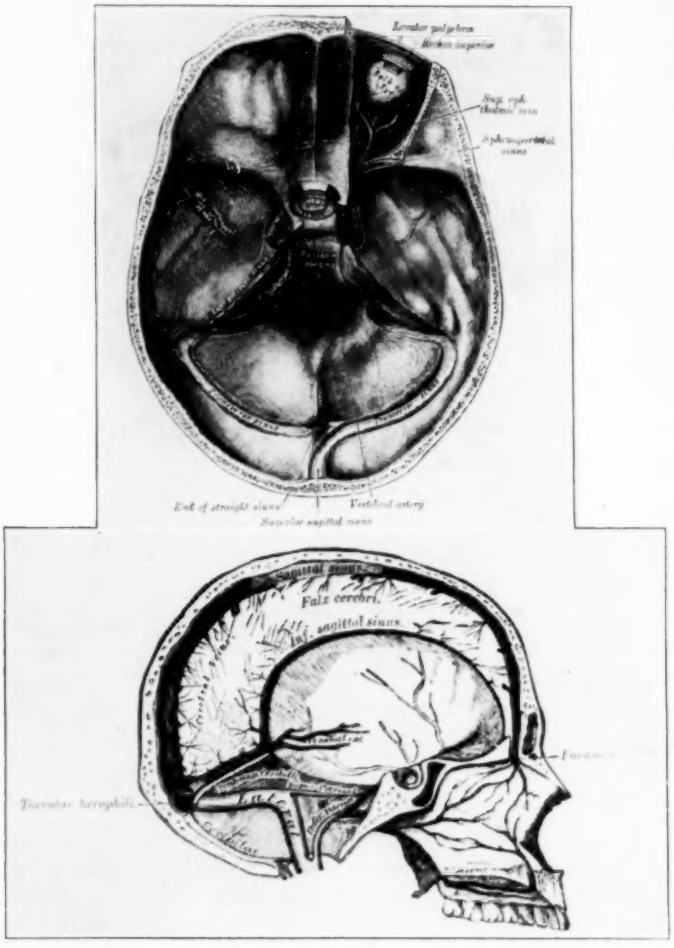

Fig. 2.—Diagrams of the cranial venous sinuses (from Gray's "Anatomy"). The upper figure gives a view of the sinuses at the base of the skull seen from above. The lower figure is a sagittal section, with the posterior cranial fossa cut lateral to the midline.

of these were specimens from the dissecting room, the remainder, specimens secured at autopsy.

The great intracranial venous tributary running into the internal jugular vein and forming its origin is the transverse or lateral sinus

(fig. 2). It is formed anterior to the occiput, either from the superior longitudinal sinus, which runs backward in the superior border of the falx from the straight sinus in the inferior border of the falx, or from a bifurcation or confluence of these two. From this point it runs forward and laterally in the layers of the attached border of the tentorium cerebelli to the junction of the petrous and mastoid portions of the temporal bone. Here it turns abruptly downward across the mastoid temporal and onto the jugular process of the occipital bone to terminate in the jugular bulb, the dilated portion of the jugular foramen, which marks the origin of the internal jugular vein.

Anterior to this venous system lie the cavernous sinuses. Their efferent flow is partly taken care of anteriorly by their communications with the ophthalmic veins, which, in turn, run through the orbit and communicate with the angular vein of the face. Posteriorly, there are two larger communications with the first great system already described. The first is the superior petrosal sinus, running backward across the crest of the petrous bone to end in the transverse sinus just after it makes its bend downward. The second is the inferior petrosal sinus, which runs backward in the dura over the suture between the petrous bone and the basi-occiput. Reaching the jugular foramen, it dips downward through its anterior portion and joins the internal jugular vein a few millimeters outside the skull. In two cases studied in the group to be described later, there was no inferior petrosal sinus on one side. In these cases the superior petrosal sinus compensated by being larger than usual.

Aside from the two tributaries of the internal jugular vein noted, i. e., the larger transverse sinus and the tiny inferior petrosal, the remainder of the outflow from the cranium takes place through smaller emissary veins, the content of which ultimately finds its way into the internal jugular vein. Examination of these veins in the study to be described discloses that they are of fairly equal size on the two sides. The transverse and inferior petrosal sinuses are, however, of unequal size, as will be shown.

METHOD

The terminal portions of both sinuses in question lie deeply embedded in the bone they traverse, forming a trough, roughly semicircular in cross-section, the base of the semicircle being directed against, and formed by, the dura, which is, in this location, extraordinarily tough and unyielding. Since the sinuses are sunken in bone, it is possible to obtain, by removing their rigid dural roofs, paraffin impressions which show accurately their size and shape. Because the mid-portion of the jugular foramen between the two sinuses is occupied by the outgoing ninth, tenth and eleventh nerves, no attempt was made to obtain an impression of the jugular bulb or the origin of the jugular vein. Warm paraffin was pressed into the sinuses and allowed to harden. On removal, the casts were sectioned at right angles to their long axes, close to the ending in the jugular bulb.

This space is just beyond the point of communication with hypoglossal and condyloid emissary veins and with the occipital sinus. The ends of the cross-sections were painted with gum gamboge and this was impressed on millimeter-ruled paper (fig. 3). These impressions gave a basis for measuring not only the width and the depth of the sinuses, but the cross-sectional area as well. The actual measure-

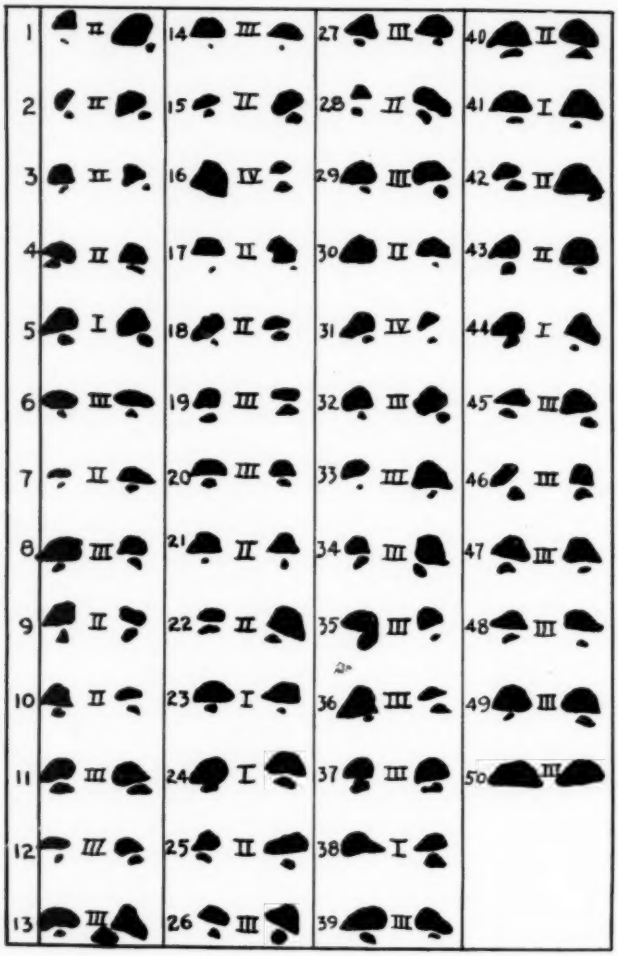

Fig. 3.—Photograph of impressions of cross-sections of sinuses (reduced). The paper is millimeter-ruled. The roman numerals indicate the type of the sinus. In each case, the transverse sinus is pictured above the inferior petrosal sinus on the left and right sides as shown.

ments of the sinuses, according to the groups to be described, are recorded in the accompanying tables. It is apparent that when the inferior petrosal sinus is small, the superior sinus is large and correspondingly increases the size of the trans-

verse sinus. The reverse is also true. In comparing cross-sections of the two sides, therefore, the combined areas of the inferior petrosal and transverse sinuses are most useful.

It was evident that the manner in which the superior longitudinal and straight sinuses ended in the transverse sinuses was of great importance. The occipital sinuses were small and varied inconsistently in number and in mode of termination; they did not seem to have any noticeable influence on the size of the trans-

TABLE 1.—*Average Combined Cross-Sectional Areas of the Transverse and Inferior Petrosal Sinuses of Each Side, According to the Type of Sinus Termination*

	Number of Cases	Left, Sq. Mm.	Right, Sq. Mm.
Type I	6	50.0	50.8
Type II (entire group)	18	33.8	44.4
Superior longitudinal to the right	11	28.4	52.6
Superior longitudinal to the left	7	42.3	31.4
Type III (entire group)	24	52.1	53.3
Larger on the right	13	37.8	51.1
Larger on the left	10	52.2	37.5
Equal	1	36.0	36.0
Type IV	2	52.5	18.5
Mean average	50	41.3	44.4
Total larger on the right	25		
Total larger on the left	21		
Total equal	4		

TABLE 2.—*Average Widths and Depths of Sinuses in Millimeters*

	Left				Right			
	Transverse		Inferior Petrosal		Transverse		Inferior Petrosal	
	Width	Depth	Width	Depth	Width	Depth	Width	Depth
Type I	10.1	6.0	3.5	1.8	10.0	6.0	3.3	2.0
Type II (entire group)	7.6	4.6	2.8	1.7	8.7	5.5	3.2	1.9
Superior longitudinal to the right	6.7	3.9	3.1	1.8	9.2	6.2	3.1	1.8
Superior longitudinal to the left	9.0	5.7	2.6	1.5	7.7	4.3	3.4	2.0
Type III (entire group)	9.2	6.2	3.2	1.8	13.0	5.4	3.6	2.2
Larger on the right	8.5	4.9	3.5	1.9	8.9	5.9	4.0	2.6
Larger on the left	10.2	6.1	3.0	1.7	9.6	5.0	3.1	1.7
Equal	9.0	4.0	2.0	1.0	10.0	4.0	3.0	2.0
Type IV	9.5	7.5	3.0	2.0	5.5	3.5	3.0	1.5
Mean average	8.7	5.2	3.0	1.7	8.9	5.4	3.4	2.0

verse sinuses. A study of the modes of termination was carried out by means of injections of paraffin and dissection. Four types of termination or "confluens sinuum" were noted, conforming fairly well to the types previously described by other authors (fig. 4).

TYPES OF SINUS

Type I: Common Reservoir.—In this type the superior and straight sinuses end in a common pool, from either side of which the

transverse sinuses arise. Testut[9] says: "The presence of the common reservoir of the classic authors exists, but is rare. Dumont found it in ten out of fifty cases examined, and it was complete only in four cases. In the other six neither the straight sinus nor the posterior occipital took the slightest part in its formation." He also quotes Manno as finding this type in two of fifty cases.

I have found this sinus in six of fifty cases, or in 12 per cent. The importance lies in the fact that the transverse sinuses arising from this type of termination are close to each other in size. The mean combined cross-sectional area on each side was almost identical. In one case the areas were identical, in two slightly larger on the right, and in three slightly larger on the left.

Type II: Unequal Deviation.—In this type the superior longitudinal sinus leans to one side or the other—ending in the transverse sinus of

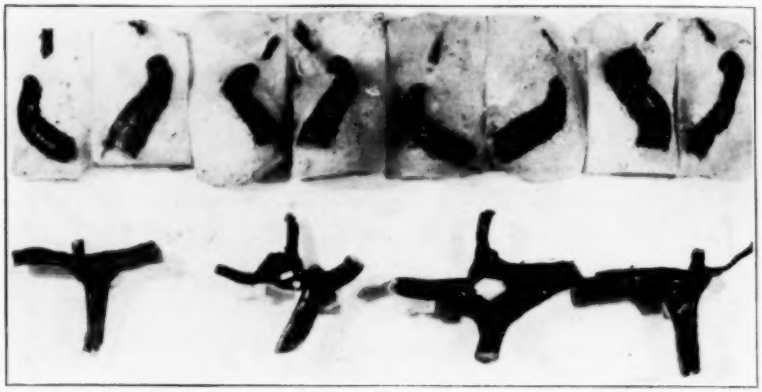

Fig. 4.—Photograph of casts of the four types of termination of the superior longitudinal and straight sinuses (below), and the transverse and inferior petrosal sinuses (above) (reduced). The superior longitudinal sinus enters the termination from below, the straight sinus from above and the transverse sinus is given off from each side. In the upper row of casts, the lower larger sinus is the transverse, the upper, the inferior petrosal sinuses. The space between is nonvenous and furnishes an exit for the ninth, tenth and eleventh cranial nerves. The types, in order, are 1, 2, 3 and 4. Note the effect of the type of sinus termination on the size of the transverse sinus of each side.

that side and sending only slender communications, if any, to the other. The straight sinus ends similarly in the transverse sinus of the opposite side.

Manno[10] found this type in fourteen of fifty cases. I have found it in eighteen, or 36 per cent. In eleven of these the superior longi-

9. Testut, L.: Traité d'anatomie humaine, Paris, Gaston Doin, 1929, vol. 2, p. 444.

10. Quoted by Testut (footnote 9).

tudinal sinus deviated to the right; in seven, to the left. In two cases the combined cross-sectional areas were equal on the two sides; in all the others, the transverse sinus was larger on the side to which the superior longitudinal sinus deviated than on the opposite side in which the straight sinus ended. This is easily understood, since the superior longitudinal is so much larger than the straight sinus.

Rüdinger [10] states: "The blood of the two lateral sinuses has then a different origin. That of the right comes entirely or for the most part from the superior longitudinal sinus, which takes its origin from the cortical veins of the hemispheres; the left, for the most part or entirely, from the depths of the brain." This conception of the difference in origin of the blood on the right and left sides has gained common acceptance, and has even been used to explain the variation in symptoms caused by tumors blocking the venous drainage on one side or another.[11] In my series, only eleven of the right transverse sinuses of this type originated in the superior longitudinal sinus as compared with seven on the left side.

Type III: Plexiform or Bifurcating Sinus.—In this type both the superior and the straight sinuses bifurcate, in equal or in unequal divisions. On either side there is a fusion of the branches to form the transverse sinus of that side. Manno found this type in thirty-four of fifty cases. I have found it in twenty-four of fifty skulls, or in 48 per cent. In these cases, the combined cross-sectional areas were larger on the right in thirteen, on the left in ten and equal in one. Rüdinger added that even in this type the two lateral sinuses are differentiated in size and the smaller carries more of the blood from the depths of the brain than the larger. I have not found any consistency in this regard. Sometimes the smaller sinus is formed mostly of a division of the straight sinus, sometimes of the superior longitudinal.

Type IV: Unilateral Deviation.—This type I am adding to the usual classification. I have found it three times, twice in this series. In this type, both the superior longitudinal sinus and the straight sinus deviate to one side (the left in all three cases observed), sending but slender communications to form the transverse sinus of the other side. In this type the greatest inequalities in the size of the transverse sinuses are found.

INFLUENCE OF THE SIZE OF THE SINUS ON JUGULAR COMPRESSION TESTS

What actual influence have the differences in size on the unilateral compression tests? In the skull is a venous reservoir, drained for the

11. Gibbs, F. A.: Relationship Between the Location of Brain Tumors and Their Manifestations, J. Nerv. & Ment. Dis. **72**:418 (Oct.) 1930.

most part by the two internal jugular veins. Jugular compression acts by obstructing a fraction of the outflow. If that fraction is the greater part of the total, the effect on the backing up of the blood and consequent rise in cerebrospinal fluid pressure will be great. Conversely, if the fraction of flow is small, the effect of backing up of blood will be small.

The resistance (h) offered to the flow of liquid, in a tube of the diameters being dealt with, may be obtained through the following formula: $h = f \frac{L}{d} \frac{v^2}{2g}$, in which f is a friction factor dependent on the type and the temperature of the liquid, the nature of the lining and the shape of the tube together with the range of pressure and velocity; L is the length of the tube; d is its diameter; v is the velocity of the liquid, and g is the acceleration caused by gravity. The friction factor is probably equal on the two sides. The acceleration of gravity is the same. The velocity will be different on the two sides and will be dependent on the common factors, i. e., the pressure and the friction factor; and on the variables, i. e., diameter and length.

This leaves two factors which vary on the two sides: (1) the diameter, which determines the area, and (2) the length. In canceling the common factors in the formula, the ability to flow, or the inverse of the resistance, is (1) directly proportionate to the diameter and (2) inversely proportionate to the length of the tube.

The quantity (Q) of blood able to flow through a given tube is the product of area and velocity, thus: $Q = a \times v$. It is true from what has been said that the velocity of the two sides will vary, but this variance is a factor of the diameter and length. One will have to be satisfied, therefore, to compare areas and length in order to determine the comparative amount of flow.

The influence of the length of tube on the resistance to the flow and the quantity varies on the two sides. Both internal jugular veins empty into innominate veins which join to form the superior vena cava, situated beneath the right side of the manubrium sterni. To reach this point, the left innominate vein has to cross the midline. To do this it must be from 2 to 4 cm. longer than the right innominate vein. That is, from the base of the skull to the superior vena cava the left jugular channel is from 2 to 4 cm. longer than the right. It follows that if the diameters of the two sides did not vary, the resistance to the flow on the left side would be greater than that on the right, and the quantity carried by the left side would be less. Further, when the diameter of the left side is less than that of the right, the factor of length increases the effect on diminution of the flow, while if the diameter on the right side is smaller, the factor of length tends to counterbalance the discrepancy.

Consideration may now be given in greater detail to the factor of diameter. The venous channel from the skull to the superior vena cava

undergoes an increase in size. This increase in diameter is dependent on the additions to the channel of blood from tributaries and corresponds fairly closely on the two sides. One may, then, from the standpoint of intracranial venous flow, deal arbitrarily with the most constantly measurable diameter of area, i. e., the combined area of the venous sinuses embedded in their osteofascial tunnel.[12]

In sinuses of type I the cross-sectional areas showed little variation in size—the average combined area on the left was 50 sq. mm. and on the right, 50.8. None of the individual cases showed sufficient variation to be of any practical importance.

In type II, there were great variations. The average for the entire group was 33.8 sq. mm. on the left and 44.4 on the right, i. e., the factor of area gave a ratio of flow on the left to that on the right of 3:4. The factor of length increased this discrepancy.

The cases of this type, in which the superior longitudinal sinus deviated to the right, gave an average of 28.4 sq. mm. on the left, and 52.6 on the right, i. e., a ratio of the flow of about 1:2.

Individual cases in this subgroup showed even greater differences. In case 1 the areas were 24 on the left and 74 on the right, i. e., a ratio in the flow of 1:3. The factor of length here, too, tended to increase the discrepancy.

In the subtype in which the superior longitudinal sinus deviated to the left, the variation in area was not as great, the ratio being 42.3 on the left to 31.4 on the right, or 1.3:1. The greatest individual difference was only 2:1, in case 10. The factor of length tended to neutralize the discrepancy in this class.

In type III the mean average gave an almost identical area on the two sides, namely, 52.1 on the left to 53.3 on the right. However, when the type was divided into subgroups, thirteen cases were found with an average ratio of 37.8 sq. mm. on the left and 51.1 sq. mm. on the right, i. e., 1:1.1. The factor of length increased this rather slight discrepancy. Individual variations rose as high as 29:60, or 1:2 (case 34). The average ratio for the subgroup in which the left side was larger gave a similar mean ratio—52.2 sq. mm. on the left to 37.5 sq. mm. on the right, but individual variations were more pronounced, as in case 36, in which the ratio was 2.5:1. The factor of length tended to diminish the discrepancy in this class.

12. If, in an actual calculation of flow, the flow for the area of the inferior petrosal and transverse sinuses is determined separately and added together, the result will vary slightly from that obtained by using the combined area as a starting point. I took note of the variation in flow occasioned by the difference in the shape of the vessel, but I do not believe that there was sufficient difference on the two sides to affect the calculation to any practical extent.

In type IV, in which the left side was predominately larger, there was a ratio of 4:1 in one case and 2:1 in the other. The factor of length was but slightly influential in reducing this great discrepancy.

These variations must be taken into account clinically. When subarachnoid block is suspected, as in a tumor of the cord, bilateral jugular compression is the procedure of choice, otherwise a low figure may result if one chances to compress a side carrying but little blood. As for unilateral compression, a negative Tobey-Ayer test has more significance than a positive one. For example, if one is confronted by a patient with bilateral otitis media who begins to show constitutional signs suggesting transverse sinus thrombosis, an adequate rise in pressure on compression on one side will allow the clinician to state with a great degree of certainty that there is no thrombosis on that side. In regard to the side showing the least response, the clinician can say only that there may be transverse sinus thrombosis.

CONCLUSIONS

1. Forty-six out of fifty, or 92 per cent, of the skulls studied had a difference in the diameter of the outgoing venous sinuses of the two sides, twenty-five being larger on the right and twenty-one on the left. Discrepancy in size may reach the ratio of 4:1. In the cases in which the sinuses were larger on the right, the variation in size was greater than when the left side was the larger. The left venous channel was always longer. The increased resistance to flow caused by this increased the amount of blood carried by the right side in cases in which the right side was the larger, and tended to diminish the discrepancy when the left side was larger.

Therefore, there is a definite anatomic basis for the fact that the mean of manometric tests shows more response to jugular compression on the right and less on the left. Individual variations occur so frequently, however, that the left side may carry much more blood than the right and may give much greater response to jugular compression.

2. Because it is true that there is an anatomic basis for a low response to the jugular compression test on one or the other side in many normal persons, a normal response has far more significance in excluding pathologic obstruction than has a poor response in indicating such an obstruction.

SCHIZOPHRENIC PSYCHOSES

CRITICAL CONSIDERATIONS OF THE PSYCHOANALYTIC TREATMENT *

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The psychodynamic approach to an understanding of mental disturbances can be considered a decisive step in psychopathology. It is due to this new point of view that psychopathology has overcome its merely descriptive stage and has become an explanatory science. The psychodynamic approach has also made it possible to influence psychopathologic processes in an intelligent and systematic way. It is worth while for a moment to review critically the work done and the methods employed. Such a critical review has proved necessary and fruitful in every science; for the investigator, submerged in daily work, too easily loses his orientation and is inclined to employ uncritically highly developed and specialized methods in the investigation of new subject matter. The danger of using highly specialized methods in the treatment of patients to whom they are not strictly applicable is even greater in the case of the therapeutist. I am alluding to the development of psychoanalysis, since this very young science has already reached a stage at which the uncritical employment of routine technic is imminent.

The psychoanalytic method of investigation and therapy was originally limited to certain cases of psychoneuroses. But the rich harvest of psychologic insight of general validity has induced psychoanalysts to apply this insight to the study of new types of cases and at the same time to test the efficiency of the analytic therapy on other mental disturbances than those to which the technic was originally applied. In the extension of psychoanalytic methods, it seems to me of great importance to distinguish between research and therapy. The employment of psychoanalytic knowledge for an understanding of mental disturbances other than the psychoneuroses is in any case legitimate and justified, whereas the employment of the same therapeutic procedure with further cases is highly problematic. Those that are of a different psychodynamic structure require modifications of the technic.

As a matter of fact, such a modification of technic proved necessary when psychonalysis was first applied to a new object, namely, to the

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study of the child. In child analysis the simple imitation of the technic used with adults was impossible for a technical reason. In analytic work one can not expect the same cooperation from a child as from an adult, and one cannot induce the child to assume the uncontrolled manner of thinking required in the method of free association. In the place of free association, Miss Klein introduced the ingenious method of the play technic.[1] She observed the playing child and interpreted the products of fantasy that it displays during spontaneous play. Except for this technical change, however, she followed the usual analytic technic of interpretation; that is, she tried to make the child conscious of the latent meaning of the manifestations of its unconscious mind. Essentially, Miss Klein's technic is based on the same therapeutic idea used in the analysis of adults, that of making conscious repressed mental contents.

Anna Freud took a more critical attitude in her technic of child analysis.[2] She considered the fact that the dynamic relation between the impulses and the ego in children is different from that in adults. The child's ego is relatively weak, but at the same time flexible. She therefore tried to influence it directly in an educational sense and also to estimate more carefully how far the weak ego of the child could be burdened with a knowledge of repressed material. The modification of the technic takes account of the special mental conditions present in the child: the relative weakness and the great flexibility of the infantile ego. I mention the technic of child analysis only as an example of the necessity of changing the technic in applying it to new and different therapeutic fields.

It is only natural that there is a demand to make use of the experiences obtained from the study of psychoneurosis in the treatment for psychoses. If one considers this problem from a superficial and merely technical point of view, it seems that the only concrete difficulty of applying the analytic technic to psychoses lies in the difficulty of rapport, and consequently in the lack of cooperation of the psychotic patient. In many cases this difficulty is only temporary, for it exists only during severe psychotic episodes. Why should not the analytic technic be tried in the intervals of remission. In these intervals the patient often displays considerable capacity for emotional rapport, or transference, and even a great desire for emotional contact with others. In such cases, the external conditions for the employment of the analytic technic are present.

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1. Klein, Melanie: Infant Analysis, Internat. J. Psycho-Analysis **7**:31, 1926.

2. Freud, Anna: Introduction to the Technique of Child Analysis, Nervous and Mental Disease Monograph Series no. 48, Washington, D. C., Nervous & Mental Diseases Publishing Company, 1928.

The most direct and simple way to decide whether a mere imitation of the treatment for a neurosis is feasible in cases of psychosis would undoubtedly be empiric. Of course, in medicine, experimentation is inherently limited by therapeutic interest in the welfare of the patient. Senseless and presumably unsuccessful or even harmful experiments must be excluded. Unfortunately, knowledge of the specific makeup of neurotic and psychotic personalities is not yet so advanced as to enable one to decide definitely with the help of merely theoretic considerations whether or not the analytic method without essential modifications is applicable in psychoses.

Actual experience, however, is still insufficient to enable one to form an opinion. This insufficiency has many causes. In the first place, up to now, most psychoanalytic treatments have been undertaken with ambulatory patients; in the case of psychoses this is generally difficult and risky. Partly for this practical reason, partly also because of theoretic considerations, the general attitude among psychoanalysts has been that a diagnosis of schizophrenia is a contraindication to psychoanalytic treatment. In recent years, however, there has been a change in this rigid attitude. In some psychiatric hospitals, for example Bloomingdale Hospital and Shepherd and Enoch Pratt Hospital in America, psychoanalysis has become an accepted method. Furthermore, Simmel, in Berlin, and Glueck, in New York, opened psychoanalytic sanatoriums for the analytic treatment of hospitalized patients. Although detailed and critical reports are still lacking, these institutions have assumed a more optimistic attitude.

In contrast to this increasingly optimistic attitude, however, are the generally known observations of experienced analysts, namely, that psychoanalytic treatment might precipitate schizophrenic episodes in patients in whom a latent schizophrenia had not been diagnosed before starting the analysis.[3] I have had occasion to observe patients in whom I could not explain the onset of an episode otherwise than as a reaction to the analytic approach. Experiences of this sort made me cautious, and without making definite theoretical considerations in all cases in which schizophrenia was suspected, but in which I nevertheless undertook psychoanalytic treatment, I changed my technic. With such a changed technic, I was able to see positive results, or at least to avoid reactive episodes. Indeed, most psychoanalysts who have reported on such treatment in psychoses agree on this one point; they have found it necessary

3. L. E. Hinsie remarked that there are only "impressionistic comments" in the literature, that psychoanalysis has a detrimental influence in the management of schizophrenic patients. The precipitating influence of the "classical technique" in cases of latent schizophrenia is, however, a well established experience. Hinsie, L. E.: The Treatment of Schizophrenia, Baltimore, Williams & Wilkins Company, 1930, p. 169.

to change the technic. Brill reported several cases in which he had good results with the help of a modified technic.[4] Zilboorg also emphasized the necessity of a "long preliminary period of reality testing," in which the analyst should gain the positive transference of the patient.[5] Moreover, I refer to Hinsie's thorough study, "The Treatment of Schizophrenia," in which he gives a rather complete review of the various modifications of the technic suggested by psychiatrists and psychoanalysts.

Psychotic reactions to the analytic approach are, paradoxically enough, not an unfavorable sign, because they show that the course of the psychosis can be influenced by psychologic influences. It is a question of secondary importance whether this influence has been favorable or unfavorable. If the essential fact is established that the course of the psychosis yields to psychologic measures, there is a theoretical possibility that by the intelligent choice of psychic measures it can be influenced favorably.

It is impossible to form a definite opinion of the possibilities of psychoanalytic treatment in the psychoses so long as reports not only do not indicate merely positive or negative results, but also do not give an exact description of the technic employed, especially of the modifications of the technic. Psychoanalytic treatment in the psychoneuroses is so highly developed and refined that one is able to give an account in a rather detailed way of the different therapeutic factors at work during the treatment. In other words, one can follow the process of the cure and know with fair precision what is going on in the mental apparatus of the patient. Psychoanalytic treatment today is by no means based only on rough empiricism, but on a detailed knowledge of the mental apparatus and of the dynamic structure of the psychoneuroses. The blind application of the psychoanalytic technic is opposed to its scientific nature, and, therefore, since one knows the basic differences in the dynamic structure of the psychoses and neuroses, one must be able at least to indicate in their main outlines the modifications of technic that necessarily follow from the difference between the psychotic and the neurotic mind. I shall limit this paper to a few essential considerations. My conclusions must be regarded merely as proposals that are still to be proved by clinical experience.

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4. It would be highly desirable if A. A. Brill would give further details as to the modifications that he mentions in his article "Schizophrenia and Psychotherapy" (Am. J. Psychiat. **9**:519, 1924).

5. The same remark is also valid for the article by G. Zilboorg, "Affective Reintegration in the Schizophrenias" (Arch. Neurol. & Psychiat. **24**:335 [Aug.] 1930). The expression that he uses, "a long preliminary period of reality testing," refers rather clearly to a modification of the technic, by means of which the usually loose relation of the schizophrenic ego to reality is reconstructed.

COMPARISON OF PSYCHOSIS AND PSYCHONEUROSIS

One may define the chief difference between a psychosis and a psychoneurosis by stating that whereas the psychoneurosis is chiefly a conflict between the different structural parts of the mental apparatus, in the psychosis the relation of the mental apparatus to the external world is disturbed in a pronounced manner. During psychotic episodes, or in progressive cases of psychosis, the patient lacks orientation to the external world because he falsifies the data of his sense perceptions. To express it simply, the psychotic person is so highly influenced by his subjective, nonadjusted demands that he cannot accept a reality which is in contrast to his subjective demands, and he falsifies the picture of the external world with which his senses and his normal thinking supply him. He sees things as different from what they really are. The most extreme form of this falsification of reality is the hallucination, but the illusion and even the delusion also have a similar meaning. This falsifying tendency has a transparent mechanism in the delusion. The psychotic patient perceives in himself unacceptable, hostile or sexual tendencies, and he simply denies these as his own mental possession: He projects them onto others. The well known resistance of such paranoic persons against every explanation, the impossibilty of convincing them of the falseness of their delusions, is based on the fact that they actually perceive a hostile or sexual emotion in themselves. Their falsification consists only in that they ascribe this emotion to a false place. They feel the presence of such emotions, but they will not admit that they belong to their own personality. So the incorrigible delusions arise, and their vividness is based on the actual introspective experience of the projected emotions. One may express this fact by saying that the psychotic person has, in a sense, no respect for reality. It is easier for him to diminish his dependence on reality than to control his own emotions. As a result of this loose relation to reality, the psychotic patient can solve his inner conflicts by changing in fantasy the picture of stubborn reality into a pseudoreality that is in accordance with his subjective demands.

I think that, having arrived at this point, it is important to distinguish between two kinds of conflicts present in psychotic persons. The first is of an infantile type and might be verbalized in the following way: "The world is not what I should like to have it. I don't want to live in such a world and therefore I prefer to live in a fantastic one; I am ready to renounce real satisfactions and content myself with fantastic hallucinatory satisfactions, if only these are what I wish." This solution of the conflict means the denial of the adjustment to the facts of external reality and leads to hallucinations, illusions and a general disorientation to the external world.

The second type of conflict produces delusions and all paranoid phenomena, and is the same as one finds in the psychoneuroses. These conflicts are no longer based on the fact that external reality is contradictory to the subjective tendencies, but on the fact that these tendencies are not acceptable to the socially adjusted part of the ego. In the psychoneuroses, hostile and sexual tendencies that are unacceptable to this socially adjusted portion of the personality, to the super-ego, are repressed from consciousness and then, disguised, return in the form of neurotic symptoms, to offer in this way a substitutive satisfaction. In the psychotic mechanisms these rejected tendencies—to be sure, not rejected by external reality, but by the super-ego—are not repressed but projected; that is, they are not recognized as belonging to one's own person, but as belonging to external reality. While the paranoid mechanisms are both falsifications of internal and external reality, the hallucinations and illusions are only falsifications of external reality. The patient with hallucinations only changes the picture of the external world, but the paranoid patient denies something that is present in himself.

TYPES OF SCHIZOPHRENIA

I think that it has now become evident that these two categories of symptoms, the simple falsification of reality and the paranoid symptoms, may supply a basis of classification for the great complexity of disturbances that we subsume under the diagnosis schizophrenia. The paranoid mechanisms are more closely allied to neurosis and show that the more highly organized portions of the mental apparatus are not yet out of action. They show the dynamic efficiency of the socially adjusted parts of the ego, for paranoid patients are not able to get rid of the influence of their super-ego. The fact that such patients project certain mental contents proves that they cannot admit them. The repression of the neurotic patient is not possible for them. Their ego is not able to exclude from consciousness ego-alien contents which the neurotic person, at least in the original form of the disease, is able to hide from himself. The psychotic person cannot repress ego-alien tendencies nor can he accept them; therefore, the only solution is projection. The psychotic person is aware of his ego-alien tendencies since he cannot repress them, and so he has to deny them as part of his own ego. Hallucinations and illusions, in general, do not presume such an inner conflict between super-ego and ego-alien tendencies; they simply are solutions of a conflict of the ego with external reality. Therefore, I called this mechanism more infantile because it corresponds to an early stage of development, in which the conflict between subjective demands and reality is not yet internalized as a conflict between subjective demands and super-ego.

Paranoid hallucinations may assume an intermediary position. In these the threats of the super-ego are projected into external reality. This is an attempt to get rid of one's own super-ego. If one remembers that the super-ego has developed by the assumption and internalizing of the moral and educational proscriptions of the parents, such paranoid hallucinations may be considered a regression to a period in which the ego was merely controlled by external persons, in which the child renounced wishes only because of fear of the forbidding and punishing parents.

But in certain cases of schizophrenia, the ego also loses its synthesizing function of bringing into harmony different and often contradictory instinctive demands. The sudden, unmotivated aggressive attacks and self-destructive behavior are clear signs of the disintegration of the structure of the ego. It seems to me unjustifiable to regard the impulsive self-mutilations of schizophrenic patients as self-punishing reactions induced by a harsh super-ego. It is impossible to assume that the same schizophrenic person who has lost fundamental functions of the super-ego, such as pity and disgust, and who indulges in coprophilic satisfactions should retain the exquisitely moral reaction of the need of punishment. The self-mutilations, although symbolic self-castrations, are rather manifestations of isolated, passive-female wishes, which find an outlet after the synthesizing function of the ego is eliminated. The polymorphous rhapsodic behavior is the manifestation of the disorganized instinctive demands that have lost their interconnections and, isolated from each other, separately seek outlets.

These considerations indicate a distinction between two great groups of schizophrenia characterized by the predominance of either paranoid symptoms (paranoid hallucinations and delusions) or simple falsifications (hallucinations and illusions). The theoretical and therapeutic evaluation of the cases with pronounced paranoid manifestations must be different from that of the cases without paranoid symptoms. The paranoid cases show a higher participation of the super-ego than do the cases belonging to the other class, which is evidence that the structure of the ego is less deteriorated. Common, however, to both types is the amazing ease with which the psychotic patient is able to give up his dependence on reality and to falsify it according to his subjective demands. The general characteristic of schizophrenia, consequently, is this faculty of getting rid of the facts of reality; this basically differentiates it from a neurosis in which such a radical flight from reality is impossible. The neurotic patient is too loyal to reality to be able to deny its objective nature. Consequently, he must fight out the conflict within his own person. The dynamic relation between the ego and instinctive demands is just the opposite in psychosis and neurosis.

In neurosis, the ego is strong and overpowers the instinctive demands. The neurotic symptom is a revolution of the restricted instincts. In psychosis the ego is weak in relation to the instinctive demands; therefore, the apparent lack, or at least weakness, of repressions. In psychosis the instinctive demands overpower the ego, and in following the pressure of these demands the ego gives up its oldest and first acquired function, the recognition of reality. But at the same time the ego also loses its other function of bringing into harmony the different instinctive demands. It turns out to be weak in both directions, toward external reality as well as toward the pressure of the primitive, unadjusted tendencies of the instinctive life.

Knowledge of the developmental phases of the mental apparatus permits a more precise evaluation of this difference between psychosis and neurosis. There are many reasons to assume that the infant's psychic processes are similar to those which adults manifest only in their dream life, and also similar to hallucinatory processes present in schizophrenic patients. Many years ago, Bleuler referred to the similarity of dream processes and schizophrenic manifestations. The differentiation between ego and non-ego is undoubtedly one of the first accomplishments in a person's development. The acceptance and replacement of the data of sense perception for hallucinatory fantasies is the basis of this distinction. Consequently, one may say that the hallucinatory psychotic patient gives up his first adjustment to external reality. This first adjustment has nothing to do with the later social adjustment, which is disturbed in the neuroses. It is simply an adjustment of the individual to the physical facts of reality. This adjustment takes place at a time when the differentiation between ego and super-ego has not yet begun It is a much earlier phase of the development of personality that occurs during the first two years after birth. One must assume that patients in whom schizophrenia later develops had not accomplished this first developmental step in a satisfactory way. In other words, one must assume that in such patients this first adjustment of the ego—the acceptance of the facts of external reality and the distinction between the ego and the non-ego—had never been firmly established.[6] Only this looseness of the relation to external reality can explain the possibility of such a radical solution of mental conflicts as occurs in psychosis. The precipitating causes of the psychosis, of course, are found in adolescent or adult life. One often observes precipitating conflicts of the same social nature that are effective in neurosis. But in his flight from the conflicts of adulthood, the psychotic person runs back to a very

6. Storch appropriately called this phenomenon "Grenzverwischung zwischen Ich und Umwelt." Storch, Alfred: Das archaisch-primitive Erleben und Denken der Schizophrenen, Berlin, Julius Springer, 1922.

early period of his life in which he was not yet able to distinguish between fantasy and reality. And it is precisely this depth of the regression that characterizes psychosis. The developmental difference between psychosis and neurosis is this, that the adjustment to reality in the former was already disturbed at a very early, more impersonal period, while in the neurosis the disturbance dates from emotional conflicts with factors in the environment—persons, parents and siblings—namely, from the period of the development of the super-ego.

The early origin of the schizophrenic symptoms allows one to make an etiologic assumption. One must assume that, in general, in schizophrenic psychoses the inherited constitution plays a more important rôle than it does in neuroses. It is difficult to imagine that external influences alone could be responsible for this early weakness of the ego which inhibits the first adjustments to the physical facts of reality, unless one finds in the majority of cases such unusual and violent psychologic influences as can explain this early rejection of reality.

I admit that the etiologic theory of the constitutional weakness of the "Ego-Anlage" is too general to be an altogether satisfactory scientific concept, but so long as there is nothing better to put in its place it may serve for a general orientation and help one to avoid overstressing the psychogenic theory of schizophrenia. Of course, in many cases, the influences of postnatal development may play an important rôle. All influences that strengthen the ego-reality relation—or to express it in a more popular way—all influences that tend to make external reality more acceptable, even for a weak ego, will decrease the efficiency of psychotic tendencies, and, vice versa, all later influences that make it difficult for the ego to accept external reality will increase the likelihood of the onset of schizophrenia. A specific etiologic theory of the schizophrenias, however, must explain why conflicts and influences of later life can drive these personalities back to such an early stage of development, in which the mental apparatus was as yet unable to distinguish between external and internal reality, between ego and non-ego. The weakness of the faculty of making this distinction cannot be explained by later influences, which occur after this distinguishing faculty has usually been acquired in normal development. Traumatic influences, even of later infancy, cannot be responsible for the weakness of a faculty, the acquirement of which belongs to an earlier phase of development. Many people do not like the world as it is, but only a few—and these are the psychotic persons—are able to deny it so radically.

APPLICATION OF THE PSYCHOANALYTIC TREATMENT

Although all these circumstances are not formulated quite so precisely, one can observe in the therapeutic endeavors of modern psychiatric

hospitals a kind of intuitive grasp of these facts. The general tendency in modern hospitals to make the environment as agreeable and as acceptable as possible to the patients is a therapeutic measure that is in harmony with the insight here developed. The positive results of occupational therapy can also be explained on the basis of these relations. If the patient finds a place that he can successfully fill, he will again be more inclined to accept at least a part of reality and to give up the flight from it. The principle of adjusting the institutional environment to the personality of the schizophrenic patient is most consistently realized in the therapeutic procedures that have been described by Sullivan.[7] He adjusted not only the physical but also the human environment to the emotional life of his patients by employing as attendants schizoid personalities who have lost their "natural conviction as to right and wrong," and who consequently have an understanding of the peculiarities of those who are psychotic. Furthermore, he gave special training to these "sensitive, shy and ordinarily considered handicapped employees" by teaching them "to cease to regard the schizophrenics in more or less traditional ideology as insane, but instead to see the many points of significant resemblance between the patient and employee." Sullivan reported unusually good results.

The principle of selecting attendants with personality traits similar to those of the schizophrenic patients is in accordance with the observations of Nunberg[8] and Landauer[9] that the reestablishment of the patient's relation to the external world is based on identification with the persons with whom he has continued contact. That such an identification comes about more easily with persons of similar type is evident. This also explains the frequent presence of pronounced homosexual tendencies in schizophrenic patients. The homosexual object relation of schizophrenic patients is a pseudo-object relation, since it is essentially a narcissistic identification.

It is now necessary, however, to make use of this insight in finding the general principles of an adequate and consistent psychotherapy for psychotic persons. That the classic psychoanalytic technic is by no means adapted to the specific conditions of the personality of the psychotic person does not need further argument. This method of cure has been found in dealing with neurotic persons and is well adapted to the psychodynamic conditions present in psychoneurosis. The problem of the neurotic personality is to regain possession of the repressed mental

7. Proceedings of the Second Colloquium on Personality Investigation, Baltimore, Johns Hopkins Press, 1930, pp. 46, 47 and 107.

8. Nunberg, H.: Der Verlauf des Libido Konfliktes in einem Falle von Schizophrenie, Internat. Ztschr. f. Psychoanal. **7**:301, 1921.

9. Landauer, K.: Spontanheilung einer Katatonie, Internat. Ztschr. f. ärztliche Psychoanal. **2**:441, 1914.

contents that his adult ego might easily control if it only knew of them. The problem of the psychotic person is different; repressions do not have to be solved, but the ego must be induced to accept external reality. The neurotic person has to learn to accept repressed psychic facts, while the psychotic person has to learn to accept rejected external facts.

In a recent brief article on denial, Freud has shown that the infantile ego accepts everything from reality that is in accord with the first libidinal demands and rejects everything that is opposed.[10] The first division between the ego and the non-ego takes place on this emotional basis. In the beginning the ego is a collection of everything that is good, acceptable, and connected with pleasure, while everything that is bad and unacceptable belongs to the non-ego. From external reality one then gradually accepts more easily the things that one loves. Probably this positive attitude toward the objects of the external world, which is called object-love in distinction from narcissistic love, is that which is less intensive in the patients in whom schizophrenia later develops. The capacity to change the narcissistic libido into the object libido is diminished in the psychotic personality, and this difficulty of building up object relations seems to be a constitutional feature of the psychotic person.

The aim of an intelligent psychotherapy consequently should be to increase the libidinal relations of the ego to the external world. How this principle is carried through in institutional treatment has already been alluded to. In psychotherapeutic treatment the consistent fostering of a positive transference will remain the most important technical therapeutic device. In a noteworthy article, Nunberg described the healing process after a catatonic episode.[8] He showed convincingly that during this healing process the physician as the object of a positive transference was the first point of crystallization in the gradually increasing acceptance of external reality. As a kind of catalyzer, the analyst concentrates in himself all the patient's positive feelings of which he is capable, and then during the process of healing the patient disperses this positive feeling from the psychoanalyst to other objects of reality. Psychotherapy for schizophrenia must be based on the systematic and intentional intensification of the positive transference, and also on the skilful steering of the further extension of positive feelings from the analyst to other objects. All further details and technical devices must be found with the help of practical experimentation. Whether the interpretation and reconstruction of repressed mental contents have a justification in the treatment of psychosis is dependent on the degree to which the psychosis is mixed with neurotic mechanisms. It seems to me evident,

10. Freud, S.: Die Verneinung, Gesammelte Schriften, vol. 11, 1923-1928, Vienna, Internationaler Psychoanalytischer Verlag.

however, that the essential psychotic process cannot be influenced by interpretations. The psychotic ego is less able to repress; therefore, it must deny and project. The therapeutic problem is not to resolve repressions but to strengthen the relation to external reality. I assume that paranoid types in general must be more accessible to psychotherapeutic methods, and also that in these cases the classic technic of interpretation in the latter part of the treatment, after a strong positive transference has been established, may play a certain rôle, because paranoid symptoms, as I have already pointed out, indicate the presence of neurotic mechanisms, that is, a conflict between wishes and the super-ego. I do not now wish to try to decide theoretically how much the original technic of interpretation can accomplish in such cases after the analyst has succeeded in establishing a strong positive transference, which is the first step in intensifying the relation of the patient to reality. This question can only be solved by systematic observation in psychiatric hospitals.

These theoretic considerations coincide with the few empiric observations which show that paranoid cases are as a matter of fact more easily influenced by psychologic procedures than are other forms of schizophrenia. In the light of these considerations one can also explain why the psychoanalytic approach, I mean by this especially interpretations, might sometimes precipitate an acute episode. Interpretations always imply a burdening of the ego. Interpretations force the patient to see an unwelcome part either of external reality or of his own personality. The weak and nonresistant psychotic ego reacts naturally to these new enforced insights by a flight into denial and falsification.

With these few suggestions of an approximate nature I have tried merely to indicate the possibility of employing psychoanalytic knowledge in the development of a psychotherapeutic method that is really adapted to the specific psychodynamic conditions present in schizophrenic patients. If I have not demonstrated more than that the simple and uncritical imitation of the treatment for neurosis is inappropriate in the case of psychosis, I feel that I have served my purpose. In outlining the general principles of a future technic in the treatment for psychosis I have avoided calling it a psychoanalytic treatment, and have used the more general expression, psychotherapy in order to emphasize that what is usually called psychoanalytic treatment is especially adapted to the psychic relations of the neurotic person. But naturally the new modified technic, the general outline of which I have here tried to suggest, can be based only on psychoanalytic insight: Psychoanalysis is the name both for the therapy and for the theoretical knowledge of the mental apparatus.

ABSTRACT OF DISCUSSION

DR. W. HEALY: I wish to express appreciation of the lucidity with which this subject was presented. Will Dr. Alexander discuss the methods of treatment of schizophrenic patients by Dr. Harry Stack Sullivan and the technic of Dr. Simmel in Berlin?

DR. FRANZ ALEXANDER: I am curious about the matter, but I do not really know anything. These psychiatrists tried to find a modified method, but no one knows just what they found. I do not think, however, that Dr. Simmel went as far as Dr. Sullivan. Sullivan did not give a theoretical plan, but only suggestions for an intuitive grasping at ingenious things. These were reported in the *Bulletin of the Society for Human Relations.* About Dr. Simmel's special technic, I can not tell much more. There is the tendency in it for the psychiatrist to come into intimate contact with the schizophrenic patient. What I have told sounds more interesting than it really is. There are general principles that I think one should follow, but details are lacking as to the method.

DR. W. HEALY: Will you tell us what Dr. Simmel did with sadists?

DR. FRANZ ALEXANDER: Dr. Simmel noticed that a traumatic neurosis was due not only to shell shock but also to the whole mental situation of the soldier toward the war—the tendency to fly from reality. The chief factor in this reaction was a hostility against the officers, not the enemy. The officer was the one who was driving the soldier into death. Dr. Simmel hypnotized these soldiers and gave them a suggestion supported by a fantom, a doll of straw hidden in the room, which he gave to them saying, "Here is your officer; do with him what you want." The soldiers tried to kill the doll and were often cured of their neurosis. Of course, this is a freudian technic applied in an ingenious way. It has little to do with psychoanalytic treatment. Even Charcot did similar things, using the face of some one. There was a famous case in a woman of anesthesia of the palm or extensor side of the hand established after boxing the ears of her son. Charcot reproduced this anesthesia by having the patient hit his fist, which was represented as a face. He detected and recognized the importance of hostility as a factor in this neurosis.

DR. A. MYERSON: This reminds me of a play, called, I believe, "Once in a Lifetime," in which there was depicted in a playwright a neurosis created by his struggle against moving picture producers. He arranged pictures of them so that he could swear at them as much as he wished, and was cured. The play was by George Kaufman, a psychoanalyst.

DR. D. GREGG: Do you apply to the physician in charge of the case Dr. Sullivan's idea that the more schizophrenic the nurse is, the better?

DR. F. ALEXANDER: A certain amount of schizophrenia is good in the nurse because her understanding of the patient is better. This is difficult to express in a mathematical manner.

DR. I. HENDRICK: Dr. Alexander has come close to the two subjects that have interested me most—psychoanalysis and schizophrenia. Some years ago, I read Anna Freud's book on "Child Analysis," and found that it applied to my method of treatment of schizophrenic patients. Later, I had a chance to talk with Anna Freud. She said that only recently she had been reading a manuscript by Melanie Klein, who worked from the id to the ego, while she worked from the ego to the id. That is the same difference that Dr. Alexander points out between the analysis of neurosis and schizophrenia. A therapeutic method should be based on an adequate understanding of the unconscious emotional life and fantasies of the patient. After that has been acquired the opportunity for correcting the disease arises. The treatment for schizophrenia is a reversal of the classic analytic technic in a way comparable to what Anna Freud does with children. Another essential point is the relationship of the psychoanalyst to the patient. The reason that psychoanalysts steered away from therapy in schizophrenia was that uniform results did not seem to be possible because of the

lack of emotional relationship between physician and patient. In my own cases, I establish a definite relationship, using different methods in different cases. At the McLean Hospital I had an interesting case in which the patient and I exchanged comments in a dream language. A definite rapport resulted. Another simple device consisted of taking the patient for a little ride, which was sufficient to symbolize her going home. With another, merely mentioning a sexual relationship caused a transference reaction. I had a most interesting case in Berlin which was not, however, carried to a finish. The relationship became clearly established, and the problem of transference that developed was emotional. The analyst becomes the representative of all the fantasies that have occupied the patient, and the problem is to solve them. The reason why one should utilize all methods that are in or outside the analytic group to increase these relationships, which Dr. Alexander has represented, is that one gains a better knowledge of what has actually occurred.

THE BLOOD-CEREBROSPINAL FLUID BARRIER IN MANIC-DEPRESSIVE PSYCHOSIS

RATIOS OF DISTRIBUTION OF BROMIDE, CALCIUM, SUGAR AND CHLORIDES *

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RATIO OF DISTRIBUTION OF BROMIDE

Most of the methods designed for the study of the barrier between the blood and cerebrospinal fluid depend on the introduction of some foreign substance into the blood and the subsequent determination of the amount that reaches the cerebrospinal fluid. For reasons that we have set forth in detail elsewhere,[1] we regard the test devised by Walter [2] for estimating the ratio of distribution of bromide in the two fluids as the most useful representative of this type of procedure. Although brought forward only a few years ago, it has already received wide recognition as a serviceable means of approach toward psychiatric problems. To the present time, however, no publications have dealt with a sufficient number of cases of manic-depressive psychosis to allow definite conclusions concerning the ratio of distribution of bromide in that disorder. Our chief purpose in this communication is to set forth the results that we obtained with Walter's method in a larger series of cases belonging to the affective group of psychoses.

As the method has already been described in detail,[3] only a short outline is given here. We have continued to use the modification of the original procedure suggested by Hauptmann.[4]

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* Read at a meeting of the Association for Research in Nervous and Mental Disease, New York, Dec. 29, 1930.

1. Malamud, W., and Rothschild, D.: Barrier Between the Blood and Cerebrospinal Fluid: III. Distribution Ratio of Bromides in Schizophrenias, Arch. Neurol. & Psychiat. **24**:348 (Aug.) 1930.

2. Walter, F. K.: Studien über die Permeabilität der Meningen, Ztschr. f. d. ges. Neurol. u. Psychiat. **95**:522, 1925.

3. Malamud, W.; Fuchs, D. M., and Malamud, N.: Barrier Between the Blood and the Cerebrospinal Fluid, Arch. Neurol. & Psychiat. **20**:780 (Oct.) 1928.

4. Hauptmann, A.: Untersuchungen über die Blut-Liquorpassage bei Psychosen, Ztschr. f. d. ges. Neurol. u. Psychiat. **100**:332, 1926.

METHOD OF PROCEDURE

An aqueous solution of sodium bromide is given in the proportion of 0.01 Gm. per pound of body weight three times daily for five days. After an interval of from eighteen to twenty-four hours, blood and cerebrospinal fluid are removed as nearly simultaneously as possible. This should be done with the patient in a fasting condition. The proteins are precipitated in both fluids, and gold chloride is added to the filtrates, thus causing the formation of gold bromide. This is yellowish brown in color, the intensity varying with the concentration of the bromide. By examining the two solutions in a colorimeter, a ratio is obtained that represents the proportion of bromide in the blood as compared to that in the cerebrospinal fluid. In normal persons the blood contains about three times as much bromide as the cerebrospinal fluid; in other words, the normal ratio of the bromide in the blood to that in the spinal fluid is 3, with fluctuations from about 2.8 to 3.2. Hence a ratio below 2.8 is indicative of an increased passage of bromide into the cerebrospinal fluid, while a determination above 3.2 denotes that less than the normal amount has reached the cerebrospinal fluid.

While the technic of this procedure is not difficult, it is important to remember that certain pitfalls may be encountered in interpreting the results. Thus it was demonstrated [1] that many somatic diseases, such as vascular disorders of the brain, toxemias and infectious conditions, brought about a definite lowering of the ratio of distribution of bromide. We also found that even the administration of typhoid vaccine for immunizing purposes generally caused an increased passage of bromide into the cerebrospinal fluid. Mehrtens and Pouppirt [5] discovered that hyperpyrexia produced by baths led to a lowering of the ratio of bromide. Fleischhacker and Scheiderer [6] showed that the first portion of fluid removed during lumbar puncture contained more bromide than the succeeding portions. We have been able to confirm their findings. In our experiments the ratio obtained from the first portion of fluid was lower than the second by from 0.04 to 0.08. The largest difference met with was 0.14. No satisfactory explanation of this phenomenon has been forthcoming. We have obviated this difficulty by always determining the bromide in the first portion of fluid removed. It is apparent that all these factors must be taken into account in every case if serious sources of error are to be avoided.

ANALYSIS OF RESULTS

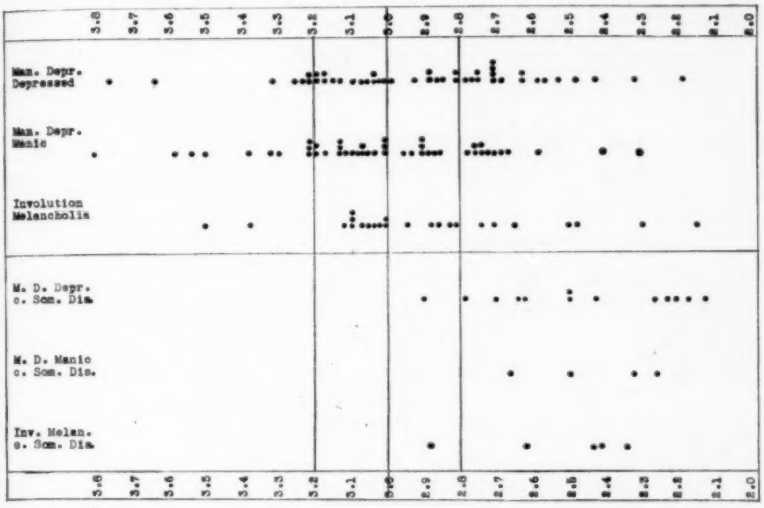
Our material comprises a hundred cases of manic-depressive psychosis, seventeen of which were reported previously,[3] and twenty-eight cases of involutional melancholia. The latter have been placed in a separate category for purposes of comparison. There were fifty-four

5. Mehrtens, H. G., and Pouppirt, P. S.: Hyperpyrexia Produced by Baths, Arch. Neurol. & Psychiat. **22**:700 (Oct.) 1929.

6. Fleischhacker, H., and Scheiderer, G.: Kritischer Beitrag zur Permeabilitätsbestimmung der Meningen nach der Walterschen Brommethode, Ztschr. f. d. ges. Neurol. u. Psychiat. **116**:692, 1928.

depressed, and forty-six manic patients, on whom, respectively, fifty-nine and fifty determinations of the ratio of distribution of bromide were made. The cases were about equally divided between the male and female sexes. The results are tabulated in the chart. In view of what has been said already in regard to the influence of various somatic diseases on the barrier for bromide, all cases complicated by such factors have been classified apart from the others. This accounts for thirteen depressed, four manic, and five involutional cases. As can be seen in the lower part of the chart, almost all of the determinations made on these patients gave values below 2.8.

On analyzing the findings in the forty-one depressed patients who showed no evidence of complicating physical factors, it can be seen


3.8 3.7 3.6 3.5 3.4 3.3 3.2 3.1 3.0 2.9 2.8 2.7 2.6 2.5 2.4 2.3 2.2 2.1 2.0
Man. Depr. Depressed
Man. Depr. Manic
Involution Melancholia
M. D. Depr. c. Som. Dis.
M. D. Manic c. Som. Dis.
Inv. Melan. c. Som. Dis.
3.8 3.7 3.6 3.5 3.4 3.3 3.2 3.1 3.0 2.9 2.8 2.7 2.6 2.5 2.4 2.3 2.2 2.1 2.0

Ratio of distribution of bromide in manic-depressive psychoses. The individual determinations are represented by dots. The figures at the top and bottom of the chart show the ratios of distribution with the line at 3 for normal.

that the ratio of distribution of bromide falls to the right of the line at 2.8 in seventeen cases, or 41.5 per cent. In other words, there is an increased passage of bromide into the spinal fluid in 41.5 per cent of this group. Values above 3.2 were found in seven cases. Four of these ratios, however, with values ranging from 3.21 to 3.23, must be regarded as borderline. There is as yet no definite agreement in regard to what constitutes the upper limit of normal. Thus Walter [7] stated that ratios of distribution up to 3.50 are normal, but von Rohden [8] refused to

7. Walter, F. K.: Die Blut-Liquorschranke, Leipzig, G. Thieme, 1929.

8. von Rohden, F.: Ueber die diagnostiche Bedeutung der Walterschen Permeabilitätsreaktion, Arch. f. Psychiat. **87**:797, 1929.

accept such a high figure. According to the latter author, values above 3.30 are indicative of an abnormally high barrier for bromide. We have continued to take 3.20 as the upper limit of normal for reasons previously stated.[8] In view of the conflicting opinions on this point, however, it would seem unwarranted to hold too closely to that figure. It was therefore not thought advisable to consider the foregoing borderline ratios as definitely high. Hence only three patients, constituting 7.3 per cent of the cases, can be said to show definitely increased ratios of distribution. This leaves 51.2 per cent of the cases with values falling within normal limits.

As regards the group of forty-two patients with uncomplicated manic-depressive psychosis, normal results were obtained in 54.8 per cent. The proportion of low values here was somewhat smaller than in the depressed group, only 28.6 per cent possessing ratios below 2.8. On the other hand, a somewhat larger number of the manic patients showed values indicative of a decreased passage of bromide into the

TABLE 1.—*Ratios of Distribution in Manic-Depressive Psychosis Summarized from the Literature*

Author	Number of Cases	Standard of Normal	Ratio of Distribution, per Cent		
			Low	Normal	High
Gordy-Smith	25	2.8 to 3.2	60.0	36.0	4.0
Hauptmann	17	2.9 to 3.3	29.0	71.0	0.0
Jacobi-Kolle	29	2.9 to 3.3	20.7	51.7	27.6
von Rohden	43	2.9 to 3.3	7.0	81.0	12.0
Walter	44	2.9 to 3.5	20.0	64.0	16.0
Rothschild-Malamud	83	2.8 to 3.2	35.0	53.0	12.0

cerebrospinal fluid, seven patients, or 16.6 per cent, having definitely high ratios.

The cases diagnosed as involutional melancholia occupied a position about half-way between the manic and depressed groups. There were twenty-three involutional cases uncomplicated by somatic disease. In eight of these cases, constituting 34.7 per cent of the total, the ratios of distribution were below 2.8. In 56.6 per cent the values were within normal limits. Only two cases, or 8.7 per cent, exhibited high ratios.

For purposes of comparison we have summarized the results from the literature in table 1. The most striking difference between our figures and those hitherto published is the larger number of low ratios of distribution obtained by us. Gordy and Smith [9] are the only authors who have found a higher percentage of cases showing an increased passage of bromide into the cerebrospinal fluid. As they did not make any mention of excluding cases complicated by somatic disease, it is

9. Gordy, S. T., and Smith, S. M.: The Permeability of the Hemato-Encephalic Barrier as Determined by the Bromide Method, Arch. Neurol. & Psychiat. **24**:727 (Oct.) 1930.

possible that this may partly account for their unusually large proportion of low ratios. The objections may justifiably be raised that none of these reports include enough cases to eliminate accidental sources of error. Furthermore, it should be borne in mind that the standard of normal varies somewhat with different authors. Hence it is difficult to make exact comparisons. The uncertainty regarding the upper limit of normal does not matter much in our group on account of the small number of cases concerned. This does not hold, however, for the lower limit. Thus with our present range of normal values, 41.5 per cent of the depressive, and 28.6 per cent of the manic, cases, making 35 per cent of the whole group, showed low values. With 2.9 adopted as the lower limit of normal, these figures would be raised to 51.2 per cent, 35.7 per cent and 43 per cent, respectively. In either case it is evident that our series shows a proportion of decreased ratios large enough to disprove the assertions of Hauptmann [10] and von Rohden [8] that the bromide method gives essentially normal results in manic-depressive psychosis.

In agreement with Jacobi and Kolle,[11] Walter [7] found that depressive conditions showed a much greater percentage of low ratios than manic ones. The same tendency was observed by us, but the difference was not striking. Von Rohden [8] attempted to discredit the results of Jacobi and Kolle on the basis that a large number of their cases exhibiting an increased passage of bromide into the cerebrospinal fluid occurred in depressions of the involutional period. His objection, however, does not apply to our results. None of the cases classified by us as depressions belonged to the involutional group. The patients were either comparatively young adults, or if older, they had had previous manic-depressive attacks. Furthermore, we have shown already that the proportion of low ratios in the involutional depressions is almost the same as in the clearcut manic-depressive group.

In view of the marked discrepancies regarding the percentage of cases with low ratios of distribution reported by different authors, it would seem of interest to examine more closely all cases in which values below 2.8 were obtained.

In the depressed group it is noteworthy that five of the six lowest ratios occurred in cases presenting the clinical picture of an agitated depression. This type of reaction was exhibited by eight patients, all of whom gave evidence of an increased passage of bromide into the cerebrospinal fluid. Their ratios of distribution ranged from 2.19 to 2.70. The divergence of this small group from the behavior of the affective

10. Hauptmann, A.: Die verminderte Durchlässigkeit der Blut-Liquor-Schranke bei Schizophrenie, Zentralbl. f. d. ges. Neurol. u. Psychiat. **48**:483, 1927.

11. Jacobi, W., and Kolle, K.: Bemerkungen zu der Arbeit von Hauptmann, Monatschr. f. Psychiat. **60**:265, 1926.

psychoses as a whole is of interest in connection with Wertham's[12] investigation of growth disorders in mental disease. He found that the frequency of growth disorders in the agitated depressions was about ten times greater than in the simple depressions. His suggestion that the distinction between these two conditions may have a wider biologic bearing is borne out to a certain extent by the uniform manner in which the blood-cerebrospinal fluid barrier acted toward bromide in the agitated patients observed by us. We were unable, however, to detect any definite correlation between the type of physical make-up and the ratio of distribution of bromide in this group of patients.

Among the manic cases, most of the lowest ratios occurred in patients who could be classified clinically as hypermanic. This observation, in conjunction with the uniformly low values obtained in the cases of agitated depression, might suggest the idea that the motor activity was one of the factors responsible for the increased passage of bromide into the cerebrospinal fluid. This is disproved, however, by the fact that the involutional melancholia group, although consisting mostly of severely agitated patients, did not show as large a proportion of low ratios as the depressed group. Furthermore, the ratios of bromide were normal in a considerable number of fairly severe manic cases.

In general, it was found that the cases with low ratios of bromide possessed certain characteristics in common. They tended to run a severe and prolonged course, as shown by the fact that the duration of the attack was longer than a year in more than half of this group. In contrast to this, less than 20 per cent of the other cases exhibited such prolonged attacks. The results of the determinations made after considerable clinical improvement had occurred showed more tendency to remain within normal limits than those made at the height of the psychosis. Thus, in the manic cases all of the ratios below 2.8 were obtained when the symptoms were at their worst. Similarly, in the depressed group only a small proportion of the determinations made during periods of improvement gave results below 2.8, the lowest being 2.67.

These findings give rise to the idea that the low ratios tend to shift upward as the clinical condition improves. This is confirmed by an examination of the results obtained when the bromide test was repeated in patients whose symptoms had begun to disappear. A glance at table 2 shows that in all but one of the cases the second ratio of distribution was considerably higher than the first. The one exception was in a patient whose first determination gave an abnormally high value. It can be seen, however, that this case possesses one feature in common with

12. Wertham, F. I.: The Incidence of Growth Disorders in Nine Hundred and Twenty-Three Cases of Mental Disease, Arch. Neurol. & Psychiat. **21**:1128 (May) 1929.

the others, i. e., the ratio of distribution approaches nearer to normal as recovery begins to take place. A similar state of affairs was observed by von Rohden [8] in three cases. The view just expressed in regard to the low ratios would seem to receive further support of an indirect nature from another angle. Thus it was possible to make second determinations of the ratio of bromide in two manic patients during subsequent manic episodes. In both cases one of the attacks was severe and the other mild. The ratios were found to be from 0.2 to 0.3 points lower in the severe than in the mild attacks. In this connection it should be mentioned that six patients belonging to the manic-depressive group were studied only after practically complete recovery from the psychosis. All showed normal ratios. While the number of cases is too small to allow definite conclusions, these findings are strongly suggestive of a tendency for the ratio of distribution to move in the direction of normal as the psychosis subsides. Such a tendency might account for some of the discrepancies in the figures

TABLE 2.—*Influence of Clinical Improvement on the Ratio of Distribution*

Name	Diagnosis	Ratio at Height of Psychosis	Ratio After Improvement
T. S.	Manic-depressive, depressed	2.42	2.80
J. K.	Manic-depressive, depressed	2.59	2.88
J. D.	Manic depressive, depressed	2.77	3.00
N. K.	Manic-depressive, depressed	2.80	2.98
R. F.	Manic-depressive, manic	3.00	3.13
L. O.	Manic-depressive, depressed	3.76	3.45

obtained by different workers. Furthermore, the fact that it was impossible to investigate many of the manic patients until their symptoms had cleared up somewhat might also account for the smaller percentage of low values for bromide found in that group than in the depressed cases. One might even venture to surmise that all manic-depressive attacks are accompanied by a change in the blood-cerebrospinal fluid barrier for bromide. It should be emphasized, however, that before any definite judgment along these lines can be reached it will be necessary to perform repeated examinations in a large number of cases.

The cases with high ratios of bromide were so infrequent that it would seem of interest to examine them more closely. Corresponding to the generally lower values found in the cases of depressions, that group exhibited a smaller number of increased ratios than the manic cases. One of the patients with a high ratio (3.53) was a woman, aged 26, who presented a fairly typical picture of a benign stupor coming on several weeks after childbirth. As this was the only example of a benign stupor investigated by us, it is impossible to do anything more than speculate on the question whether or not such cases may

occupy a special position in regard to the barrier for bromides. Apart from this, high values occurred during the first attack of mental disorder in only two cases; both were manic patients who presented some atypical features. Only one case, however, could be followed for any length of time. This was in a young woman with a ratio of bromide of 3.58. She had had a long period of depression leading to an acute excitement during which the bromide test was performed. This was replaced by a depressed state characterized by marked hypochondriacal tendencies and feelings of inferiority, without retardation. Her psychosis has continued for more than three years.

All the other patients exhibiting a decreased passage of bromide into the cerebrospinal fluid had had many previous attacks of mental disorder. Two of the high ratios (3.30, 3.39) occurred in patients who had formerly been excessively alcoholic. One was in a manic state, and the other was depressed. There is a good deal of evidence (Hauptmann,[13] von Rohden [8]) pointing to the fact that the barrier for bromide is sometimes raised in chronic alcoholic conditions. This may account for the high figures in these two cases, neither of which showed any unusual clinical features. The patients in the other cases were mostly of the type that remained mildly depressed or in a chronic hypomanic state during the intervals between the severer attacks. These patients, however, did not present any evidence of schizoid traits, in contrast to most of von Rohden's patients with high ratios. Furthermore, we were unable to confirm his statement that the physical make-up in most of the cases belonging to this group varied from the pyknic type usually met with in manic-depressive psychosis; for while the impression was gained that a slightly smaller proportion of our patients with high ratios was of a pyknic make-up than the others, the difference was not marked enough, nor was the size of the group large enough, to arrive at any definite conclusions along these lines.

In view of these findings, high ratios of distribution of bromide would seem to indicate a rather unfavorable prognosis in that they are apt to occur in patients subject to frequently recurring attacks with practically no normal periods intervening. Apart from this, the ratio of distribution of bromide in manic-depressive psychosis is of no value as a prognostic sign. Recovery from the individual acute attacks took place regardless of the state of the blood-cerebrospinal fluid barrier as revealed by the bromide test. Moreover, chronic cases occasionally exhibited normal or low figures.

It is worthy of mention that the results obtained in involutional melancholia corresponded closely to those in manic-depressive psychosis.

13. Hauptmann, A.: Zur Pathogenese alkoholischer Geistes- und Nervenkrankheiten an der Hand von Untersuchungen über die Blut-Liquorschranke, Deutsche Ztschr. f. Nervenh. **100**:91, 1927.

This would seem to lend support to the idea that the two conditions are intimately related, if not identical. It also adds further confirmation to the view that increasing age of itself does not affect the ratio of distribution of bromide. No correlation was observed in the involutional cases between the barrier for bromide and the severity of the clinical picture. While the two patients with high ratios of distribution failed to improve after three years, they did not exhibit any unusual clinical features. Five patients in this group showed marked improvement or complete recovery. Their ratios were all within normal limits. A normal barrier would therefore seem to be a somewhat favorable prognostic sign in involutional melancholia.

We cannot agree with the statement of Gordy and Smith [9] that "the Walter bromide method does not appear to afford distinct aid in the differential diagnosis of mental disease, especially as between dementia praecox and manic-depressive psychosis." On the contrary, we believe it to be of some help in distinguishing manic-depressive psychosis from schizophrenia as well as from other abnormal mental conditions. This can be seen from a glance at table 3. In all cases the final diagnosis was made only after the clinical course had been followed for a prolonged period, many of the patients in this group having been observed for several years. It is apparent that as regards manic-depressive psychosis the procedure is of more value in a negative than a positive sense. High ratios are so uncommon in affective psychoses as compared to others, particularly schizophrenia, that a high ratio in a doubtful case is strongly suggestive of some disorder other than manic-depressive psychosis. Low ratios, however, do not occur in a sufficiently large proportion of affective conditions to be of positive diagnostic worth, although they are of aid in excluding a schizophrenic process. The case at the bottom of table 3 shows that an increased passage of

TABLE 3.—*Differential Diagnostic Value of the Ratio of Distribution of Bromide*

Name	Ratio	Original Diagnosis	Final Diagnosis
R. K.	2.82	Schizophrenia	Manic-depressive (depressed)
R. G.	2.52	Schizophrenia	Manic-depressive (depressed)
E. L.	2.98	Schizophrenia	Manic-depressive (mixed)
E. S.	2.70	Schizophrenia	Manic-depressive (depressed)
H. L.	2.94	Schizophrenia	Manic-depressive (depressed)
P. J.	3.60	Manic-depressive (manic)	Schizophrenia (catatonic)
J. K.	3.48	Manic-depressive (manic)	Schizophrenia (catatonic)
F. S.	3.30	Manic-depressive (manic)	Schizophrenia (catatonic)
H. U.	3.38	Manic-depressive (manic)	Schizophrenia (catatonic)
V. B.	3.36	Manic-depressive (manic)	Schizophrenia (catatonic)
C. L.	3.83	Manic-depressive (manic)	Schizophrenia (catatonic)
B. F.	3.64	Manic-depressive (manic)	Schizophrenia (catatonic)
M. A.	3.79	Manic-depressive (depressed)	Schizophrenia (simple)
C. B.	3.58	Manic-depressive (manic)	Paranoid condition
J. H.	3.47	Manic-depressive (hypomanic)	Psychopathic personality
D. B.	3.86	Manic-depressive (hypomanic)	Psychopathic personality
A. O.	4.20	Manic-depressive (depressed)	Psychopathic personality
R. M.	3.75	Manic-depressive (hypomanic)	Psychopathic personality
E. R.	3.42	Manic-depressive (depressed)	Mental deficiency
W. W.	2.08	Manic-depressive (manic)	Toxic psychosis

bromide into the cerebrospinal fluid may occasionally help in the detection of a toxic psychosis that simulates a manic-depressive disorder. Here, however, the ratio must be very low to be of any value, as it has been demonstrated already that low values are frequently obtained in affective psychoses.

RATIOS OF DISTRIBUTION OF CALCIUM, SUGAR AND CHLORIDES

Since Walter's method deals with the distribution of bromides only, the results that it yields may not be really representative of the condition of the blood-cerebrospinal fluid barrier in a broad sense. A change in the barrier for bromide is not necessarily indicative of similar changes in regard to other substances. In fact, if the cerebrospinal fluid is a secretion, as some authors believe, it would not be surprising to find the selective activity of the barrier altered toward certain substances only. Fleischhacker and Scheiderer [14] have already brought forward evidence that the passage of bromide into the spinal fluid may be increased or decreased independently of the behavior in this respect of some of the normal constituents of the blood. On the other hand, if we are dealing with a dialysate, the unequal distribution of a new electrolyte such as bromide would probably necessitate some readjustment of the equilibrium existing between the ions in the spinal fluid and those in the blood. In view of these considerations, it is apparent that the barrier separating these two fluids should be studied from many different angles before formulating any general conclusion as to its functional state.

We have therefore thought it advisable to supplement the bromide test by making parallel determinations of the blood and spinal fluid concentrations of substances normally present in those fluids. Calcium, sugar and chlorides were selected as the most convenient for our purposes. Sufficient quantities of blood and spinal fluid for all the determinations were removed at the time of collecting the specimens for the bromide test. The method used for calcium was the Clark-Collip modification of the Kramer-Tisdall procedure.[15] Sugar was estimated by the method of Folin,[16] and chlorides by the Van Slyke

14. Fleischhacker, H., and Scheiderer, G.: Ueber die "Permeabilitätsquotienten" für Calcium, Chlor (Gesamthalogene) und Brom und ihre gegenseitigen Beziehungen bei endogenen Geisteskrankheiten, Monatschr. f. Psychiat. u. Neurol. **75:** 346 (May) 1930.

15. Clark, E. P., and Collip, J. B.: A Study of the Tisdall Method for the Determination of Blood Calcium with a Suggested Modification, J. Biol. Chem. **63:**461, 1925.

16. Folin, O.: The Determination of Sugar in Blood and Normal Urine, J. Biol. Chem. **67:**357, 1926.

procedure.[17] The ratios of distribution were obtained by dividing the blood values by the spinal fluid concentration of the substances in question.

As this work was only undertaken recently, the number of patients on whom combined determinations were made is much smaller than the number investigated by the bromide method alone. The data are presented in table 4. The ratio of distribution of calcium was determined in twenty-four cases. Fleischhacker and Scheiderer[14] stated that the normal range lies between 1.8 and 2.2. This is in accord with the generally accepted view that the cerebrospinal fluid contains about half as much calcium as the blood serum. In exactly two thirds of our cases the ratios were within the limits of from 1.8 to 2.2. There were four determinations in which values above 2.2 were obtained and five in which they were below 1.8. Thus 33.3 per cent of the group showed somewhat abnormal ratios of calcium. Weston and Howard[18] investigated twenty-seven cases of manic-depressive psychosis, without, however, calculating the ratio of distribution of calcium. An examination of their figures from this point of view shows that a considerably smaller proportion of their cases exhibited abnormal ratios of calcium. Fleischhacker and Scheiderer[14] obtained essentially normal values in affective disorders, but their material included only six cases of manic-depressive psychosis.

In two cases it was possible to repeat the whole series of determinations after marked clinical improvement had occurred. A glance at table 4 shows that as the psychosis subsided there was a tendency for the ratio of distribution of calcium to move in the direction of normal. This would seem to coincide with the observations in the ratios of bromide as has been reported already. In the remaining cases we were unable to detect any definite relation between the ratios of calcium on the one hand, and the type or severity of the symptoms on the other.

It can be seen from table 4 that almost all the abnormal ratios of calcium occurred in patients whose ratios of bromide were within normal limits. In this connection it should be remembered that these deviations in the values for calcium are not necessarily indicative of a change in the blood-cerebrospinal fluid barrier, for they may have been due to a modification in the ratio of diffusible to nondiffusible calcium in the blood. According to Cantarow,[19] the calcium content of the

17. Van Slyke, D. D.: The Determination of Chlorides in Blood and Tissues, J. Biol. Chem. **58**:523, 1923.

18. Weston, P. G., and Howard, M. Q.: The Determination of Sodium, Potassium, Calcium and Magnesium in the Blood and Spinal Fluid of Patients Suffering from Manic-Depressive Insanity, Arch. Neurol. & Psychiat. **8**:179 (Aug.) 1922.

19. Cantarow, A.: The Diffusibility of Calcium in Bronchial Asthma and Allied Disorders, and in Pulmonary Tuberculosis, Am. J. M. Sc. **179**:497 (April) 1930.

TABLE 4.—*Comparison of Ratios of Distribution of Calcium, Sugar, Chlorides and Bromide*

Name	Diagnosis	Serum Calcium, Mg. per 100 Cc.	Spinal Fluid Calcium, Mg. per 100 Cc.	Ratio of Distribution of Calcium	Blood Sugar, Mg. per 100 Cc.	Spinal Fluid Sugar, Mg. per 100 Cc.	Ratio of Distribution of Sugar	Blood Sodium Chloride, Mg. per 100 Cc.	Spinal Fluid Sodium Chloride, Mg. per 100 Cc.	Ratio of Distribution of Chloride	Ratio of Distribution of Bromide
A. C.	Manic-depressive, agitated depressed.....	11.5	6.2	1.85	....	....	....	552.2	687.1	0.80	2.13
S. B.	Manic-depressive, depressed	13.0	6.6	1.97	71.5	68.0	1.05	582.6	700.0	0.83	2.17
E. B.	Manic-depressive, depressed	9.3	4.8	1.94	....	....	....	602.6	725.4	0.83	2.25
C. B.	Manic-depressive, manic	10.4	5.0	2.08	69.0	51.5	1.35	606.1	739.4	0.82	2.40
J. K.	Manic-depressive, depressed	11.0	5.0	2.20	85.0	62.0	1.37	557.0	700.0	0.795	2.59
		11.4	5.6	2.04	....	....	....	.....	.....	....	2.88
M. H.	Manic-depressive, depressed	10.1	5.0	2.02	....	....	....	591.0	732.4	0.80	2.62
M. K.	Manic-depressive, depressed	10.8	5.2	2.08	....	....	....	586.2	703.2	0.83	2.70
E. S.	Manic-depressive, agitated depressed.....	9.0	5.9	1.53	90.0	51.1	1.76	599.0	725.0	0.82	2.70
D. M.	Manic-depressive, depressed	10.3	5.5	1.87	85.8	53.0	1.62	.....	.....	....	2.70
F. W.	Manic-depressive, depressed	11.0	5.1	2.15	105.0	83.0	1.27	.....	.....	....	2.70
E. S.	Involutional melancholia	11.1	5.4	2.06	80.0	59.0	1.36	.....	.....	....	2.73
H. M.	Manic-depressive, manic	11.8	5.2	2.27	85.0	67.0	1.27	.....	.....	....	2.73
R. K.	Manic-depressive, manic	11.8	5.3	2.23	....	....	....	.....	.....	....	2.83
S. B.	Manic-depressive, depressed	11.1	4.7	2.36	103.6	48.7	2.13	587.0	714.0	0.82	2.88
M. W.	Manic-depressive, manic	11.0	5.8	1.89	79.0	66.0	1.19	597.0	729.0	0.82	2.92
P. K.	Manic-depressive, depressed	11.4	4.5	2.50	105.0	48.8	2.15	587.0	734.0	0.80	2.94
H. L.	Manic-depressive, manic	10.4	5.6	1.86	83.3	54.0	1.54	618.0	718.0	0.86	2.97
J. D.	Manic-depressive, depressed	11.2	5.2	2.15	77.0	66.1	1.17	.....	.....	....	3.00
B. G.	Manic-depressive, manic	12.1	6.1	1.98	89.0	44.4	2.00	591.0	720.0	0.82	3.00
R. F.	Manic-depressive, manic	10.4	6.8	1.53	66.0	66.0	1.00	572.0	724.0	0.79	3.00
		9.3	5.0	1.75	83.3	45.0	1.85	657.0	737.0	0.89	3.13
C. D.	Manic-depressive, depressed	10.1	5.9	1.71	....	....	....	581.0	716.0	0.81	3.09
F. G.	Manic-depressive, manic	8.0	4.7	1.70	101.5	87.0	1.17	.....	.....	....	3.19
H. S.	Manic-depressive, manic	10.6	5.1	2.08	90.9	60.5	1.60	.....	.....	....	3.39
N. A.	Manic-depressive, manic	10.8	6.0	1.80	80.0	50.0	1.60	.....	.....	....	3.55

spinal fluid accurately represents the amount of diffusible calcium in the blood, providing the barrier between the two fluids is normal. Hence the abnormal findings might have been produced by alterations in the serum calcium leading to an increase or decrease in the diffusible fraction. This brings up the possibility of a disturbance of the calcium balance in manic-depressive psychosis. Although such a possibility is of considerable interest, it cannot be adequately discussed until a large number of cases are investigated during the free intervals as well as during the psychotic attacks.

It is of interest that all the patients with high ratios of calcium exhibited values for bromide that were a little on the lower side of 3.0. Furthermore, the group with values for bromide below the latter figure included almost all the patients with ratios of calcium above 2.0. On the other hand, rather low ratios of calcium were found in all but one of the patients showing values for bromide higher than 3.0. Thus in these patients the average of the ratios of calcium was 1.80, whereas it was 2.05 in the first mentioned group. In the absence of complete details regarding many of the substances contained in the blood and spinal fluid it would seem unwise to go into the question whether or not these findings are indicative of some inverse relationship between the values for calcium and bromide. As a matter of fact, it is not certain that the figures are striking enough to be of definite significance. Moreover, it must be admitted that the data are only suggestive when the cases are divided into two groups and examined as such. If the cases are scrutinized individually, no constant relation between the ratios of bromide and calcium can be observed.

It does not lie within the scope of this article to discuss the question of absolute calcium values in manic-depressive psychosis. Here our lack of normal standards is a definite drawback, whereas in dealing with relative quantities it is not of such importance. In view of this fact it would not seem advisable to formulate any conclusions as to the absolute values obtained in this series. It can be seen from table 4, however, that there is no correlation between the calcium content of the spinal fluid and the ratios of distribution of bromide.

The amount of sugar was determined in nineteen of the cases that were examined for calcium and bromide. The data are arranged in the middle portion of table 4. As sugar is considered freely diffusible, one might expect its ratio of distribution to be of some value in detecting changes in the blood-cerebrospinal fluid barrier. It is difficult, however, to interpret the results because of the lack of agreement as to what constitutes the normal ratio of distribution of sugar. A number of authors have stated that the sugar content of the spinal fluid is a little more than half that of the blood. Thus, according to Weich-

mann,[20] the spinal fluid contains from 54 to 68 per cent of the plasma sugar; according to Dietel,[21] from 45 to 62 per cent. Wittgenstein[22] expressed the belief that the sugar content of the spinal fluid is from 50 to 80 per cent of that of the blood. These various values represent ratios of sugar in the blood to that in the spinal fluid ranging from 1.85 to 1.47, from 2.22 to 1.61 and from 2.00 to 1.25, respectively. On the other hand, Fremont-Smith and Dailey[23] showed that alterations in the blood sugar level are reflected in the spinal fluid only after a latent period, by which time the blood sugar may have fallen to below the spinal fluid sugar level. They therefore concluded that no statement could be made as to the normal ratio of spinal fluid sugar to blood sugar.

In view of these facts, little would be gained by attempting to classify our determinations as definitely high, normal and low. Nevertheless, a few details are perhaps worthy of attention. Most of the lowest as well as the highest ratios of sugar were found in the group with normal values for bromide. Thus, four of the five lowest values for sugar, ranging from 1.00 to 1.19, occurred in this group; two of these cases also showed low ratios of calcium. Similarly, the two highest ratios of sugar (2.13, 2.15) were obtained in cases with normal figures for bromide. Both showed high values for calcium (2.36, 2.50). Apart from these instances there was no apparent parallelism between the ratios of distribution of sugar and calcium. In the individual cases the ratios of sugar did not exhibit any constant relation to the values for bromide. Yet it may be observed that in the first eight cases, all of which had low ratios of bromide, the average of the ratios of sugar was 1.38. The average figure in the remaining cases was 1.58. In other words, the cases that gave evidence of an increased passage of bromide into the spinal fluid, taken as a group, showed a slightly greater proportion of sugar in the spinal fluid than the group with normal and high ratios of bromide. The difference, however, is not marked, and our material is not large enough to warrant any definite conclusions as to the general significance of this finding.

As regards the ratio of distribution of chloride, the determinations gave essentially negative results. According to Leipold,[24] the normal

20. Weichmann, cited by Walter, F. K.: Die Blut-Liquorschranke, Leipzig, G. Thieme, 1929.

21. Dietel: Untersuchungen über das Verhältnis vom Blut- und Liquorzucker und über den diagnostischen Wert der Liquorzuckerbestimmung, Ztschr. f. d. ges. Neurol. u. Psychiat. **95**:563, 1925.

22. Wittgenstein, A.: Deutsche med. Wchnschr. **49**:246, 1923.

23. Fremont-Smith, F., and Dailey, M. D.: Cerebrospinal Fluid Sugar, Arch. Neurol. & Psychiat. **14**:390 (Sept.) 1925.

24. Leipold, W.: Durchlässigkeitsverhältnisse der Blutliquorschranke, Inaugural Dissertation, Greifswald, 1928.

ratio of distribution of chlorides is from 0.78 to 0.85. This is in accord with the generally accepted absolute values for chloride of from 570 to 620 mg. (expressed as sodium chloride) per hundred cubic centimeters in the blood plasma, and from 720 to 750 mg. per hundred cubic centimeters in the spinal fluid. Table 4 shows that all but two of the ratios were within the limits of from 0.78 to 0.85, regardless of the fact that the absolute chloride content of the blood and spinal fluid was abnormal in a few instances. It is evident that in this series of cases variations in the blood chlorides are reflected accurately in the chloride content of the spinal fluid. No significance can be attached to the two high figures, which are too near the borderline to be regarded as pathologic. There was no relation between the ratios of chloride on the one hand, and the ratios of calcium, sugar and bromide on the other. As bromide was administered to all these patients, it should be remembered that the method used for the determinations of chloride really measures the total amount of halogens. Hence the discovery of normal ratios of chloride in cases with decreased ratios of bromide confirms the statement of Fleischhacker and Scheiderer [14] that the passage of bromide from the blood into the spinal fluid takes place independently of the ratio of distribution of halogen and the absolute values for halogen.

The data available at present would seem to be too inconclusive to allow detailed discussion of the much debated question whether the cerebrospinal fluid is a secretion or a dialysate. With the exception of the few doubtful points already brought out, most of the results would seem to suggest that the blood-cerebrospinal fluid barrier acts differently toward bromide than toward calcium, sugar and chlorides. Furthermore, it is evident that there is no relation between the ratio of distribution of bromide and the quantity of protein in the spinal fluid, for in all our cases the colloidal gold curve and the usual tests for albumin and globulin were essentially normal. Nevertheless, it would be unjustifiable to conclude that bromide occupies a solitary position with respect to the blood-cerebrospinal fluid barrier until comparable experiments are made with other foreign substances.

As to the significance of the figures for bromide reported here, there is some evidence that the low ratios move upward as the clinical condition improves. It has also been demonstrated that a shifting of the ratio of bromide may take place even when the original determinations were not below normal. Reference has already been made to the frequency with which low ratios were obtained at the height of the psychosis. In view of these findings, it is probable that alterations in the blood-cerebrospinal fluid barrier for bromide are very common in manic-depressive attacks. This suggests the possibility that affective disorders may be associated in some way with as yet unknown

physical factors or bodily changes. Whether or not such factors occur regularly in manic-depressive psychosis can be determined only by further investigations in which particular emphasis is placed on repeated examinations in the individual cases.

SUMMARY

The results of a study of the blood-cerebrospinal fluid barrier by Walter's bromide method in a hundred cases of manic-depressive psychosis and twenty-eight cases of involutional melancholia are reported.

In manic-depressive psychosis, uncomplicated by somatic disease, 35 per cent of the cases showed ratios of distribution of bromide that were below 2.8, and hence indicative of an increased passage of bromide into the cerebrospinal fluid. The ratios were normal in 53 per cent of the cases and high in 12 per cent.

A larger proportion of low determinations were found in the depressed than in manic cases, 41.5 per cent of the former and 28.6 per cent of the latter exhibiting ratios of bromide below 2.8.

There was a tendency for low ratios of bromide to occur in cases in which the psychosis is particularly severe and prolonged. The cases of agitated depression all showed low ratios.

High ratios of bromide were found in 7.3 per cent of the depressed cases, and in 16.6 per cent of the manic group.

High values for bromide were apt to occur in patients subject to numerous attacks; such patients generally remained in a mildly hypomanic or depressed condition during the intervening periods.

The ratios tended to move in the direction of normal as the psychosis subsided.

In involutional melancholia, uncomplicated by somatic disease, 35 per cent of the cases showed low ratios of bromide, 56.5 per cent normal ratios, and 8.5 per cent high ratios.

The determination of the ratio of distribution of bromide is of value in the differential diagnosis of mental disease, especially as between manic-depressive psychosis and schizophrenia.

The ratios of distribution of calcium, sugar and chloride between the blood and cerebrospinal fluid were determined in a number of the patients on whom the bromide test was performed.

The ratio of distribution of calcium was abnormal in 33.3 per cent of the cases, almost all of which showed normal values for bromide.

There was a tendency for the cases with low ratios of bromide to show as a group a slightly greater passage of sugar into the spinal fluid than the group with normal or high ratios of bromide.

The ratio of distribution of chloride was normal in manic-depressive psychosis.

In the individual cases there was no constant relation between the ratios of distribution of bromide, calcium, sugar and chlorides.

Abstracts from Current Literature

CHANGES IN THE CENTRAL NERVOUS SYSTEM IN SEPTIC PYEMIA. G. KOBAYASHI, Arb. a. d. neurol. Inst. a. d. Wien. Univ. **32**:231 (Oct.) 1930.

Five cases were studied clinicopathologically.

CASE 1.—In a boy, aged 15, pain in the left hip had developed at the age of 13. This soon disappeared and he remained well for two years; then the pain recurred. On admission to the hospital, he had a temperature of 40 C. (104 F.) and râles over both lungs. Two days later, delirium developed, the cardiac action became feeble, and the patient died twelve days after the onset of the illness. Necropsy revealed: osteomyelitis of the left ilium, with pus in the left hip joint; pyemia; renal and pulmonary abscess; recent suppurative tonsillitis; parenchymatous degeneration of the liver and acute swelling of the spleen, and fibrinous pleurisy at the base of the right lung. Bacteriologic examination showed a staphylococcus pyemia, apparently of recent origin. The nervous system presented the following changes: 1. Diffuse edema of the meninges, with a serous exudate and occasional hemorrhages, but without pus cells. 2. Swelling of the cells of the intima of the blood vessels, with perivascular edema. In many areas throughout the brain there were definite evidences of perivascular disintegration, although the glia still remained intact; the condition resembled a status cribrosus and in some areas of the cerebral and cerebellar cortex appeared as an intensification of the edema. 3. Diffuse and severe degeneration of the ganglion cells. Some of the cells appeared swollen, homogeneous and pale, with some of the nuclei still remaining normal while others showed marked destruction. The dendrites also appeared swollen and vacuolated, some of them like a cork-screw. The most severe changes in the dendrites were observed in the cells of the olive and dentate nucleus, in both of which the tigroid substance in the cells had been reduced to fine granules. In Cajal preparations some of the axons also appeared swollen. The glia was only slightly increased in the marginal zone, in the glial marginal layer, in the subependyma and in some of the vessels of the striatum; there was an indication of an early glial network formation in the cerebellum. It seems, however, that the glia was also affected, because many of its cells were shrunken and completely homogeneous, with unusually small, pointed prolongations. Some of the sections showed cocci within the tissues, although in some areas it was difficult to determine whether the tissues contained cocci or the products of granular degeneration.

CASE 2.—A woman, aged 24, was admitted to the dermatologic clinic with acute cystitis, furunculosis and sepsis. Five days after admission, a temperature of 37.9 C. (98.2 F.) developed and the patient refused food; she died two days later. Necropsy revealed endometritis, cystopyelitis pseudomembranacea with bilateral pyelonephrosis, and general furunculosis. Smears from the spleen, uterus and furuncles showed gram-positive diplococci only in the uterus, and on culture Staphylococcus pyogenes-aureus, hemolytic streptococci and Bacterium coli were also recovered from the spleen. Examination of the nervous system revealed diffuse dilatation of the meninges, especially of the spinal cord, with degenerative changes in the connective tissue fibrillae and enormous dilatation of the veins, which were completely filled with blood, and slight changes in the intima. The most striking changes were seen in the walls of the subependymal arteries. The ganglion cells were swollen and showed tigrolysis, especially in the olives in which a normal cell could hardly be seen. The spinal cord seems to have been least affected, although even here the small cells appeared somewhat shrunken. The glial reaction was relatively slight but definite.

CASE 3.—In a woman, aged 76, suppurative parotitis developed, with vomiting and slight fever, which persisted for twelve days; then she suddenly became

jaundiced and unconscious. She was admitted to the hospital in a state of coma, with rigidity of the neck, a positive Babinski sign on the left and a suggestive one on the right, and cyanosis with poor circulation. A smear from the parotids yielded gram-positive diplococci and a culture yielded Staphylococcus pyogenes-aureus. Death occurred one day after admission. Necropsy revealed pockets of greenish pus in both parotids, an abscess of the bile ducts in the right lobe of the liver, gallstones, parenchymatous degeneration of all organs and an acute swelling of the spleen. Neurohistologic examination showed: venous stasis of the pia, with here and there small foci of infiltration, and swelling of the fibrillar connective tissue only in the spinal cord. In spite of the patient's advanced age, the vessels were remarkably thin, without calcification, and, except for hyperemia, showed no evidences of degeneration. The spinal cord showed homogeneization with relatively slight perivascular disintegration, and the white substance was more edematous than the gray. The ganglion cells showed diffuse changes, with relatively slight fatty degeneration, but nothing like the shrinkage and homogeneization that is usually observed in senility. The most striking changes were seen in the Purkinje cells of the olive and dentate nucleus. The anterior horn cells in the caudal portion of the spinal cord showed axonal degeneration. The glia was more fibrous than cellular. No large hemorrhages or softenings were observed.

Case 4.—In a woman, aged 21, six weeks after a normal parturition, severe headache, nausea and vomiting with edema of the eyelids suddenly developed. The edema soon became generalized, and in spite of every known therapeutic endeavor, she became gradually worse and died five months after the onset of the illness. Necropsy revealed: lipoid nephrosis, edema, anasarca, right hydrothorax, hydropericardium, ascites, edema of the brain and leptomeninges, catarrhal rhinitis, acute hemorrhages secondary to pneumomycotic septicemia, superficial erosions of the skin of the genitals and perineum infected with pneumococci, and broncho-pneumonia of the middle and lower lobes of the right lung. The dura over the brain was tense, and the leptomeninges as well as the underlying substance of the brain were very soft. Smears from the labia majora showed leukocytes, diplococci, streptococci and plump gram-positive rods. In this case the most striking histologic changes were observed in the blood vessels, especially of the striatum, in which numerous pseudocalcified deposits were found in the walls of the vessels as well as in the substance of this nucleus. The cerebral cortex and striatum contained many areas of perivascular disintegration. No hemorrhages were seen. The changes in the ganglion cells were similar to those described in cases 1, 2 and 3, but were not as marked in the dentate nucleus and olive as in the cerebral cortex where they were homogeneous, darkly stained, shrunken and devoid of nuclei. The glial reaction was also somewhat more marked in this case, although no nodular formations were observed. There were no abnormal glia cells and no glial degeneration.

Case 5.—In a boy, aged 10, a staphylococcus pyemia following an abscess in the lower jaw developed while he was being treated for a dental infection. He soon showed evidences of a severe generalized metastatic pyemia and died ten days after the onset of the illness. Necropsy revealed: acute suppurative periostitis of the entire lower jaw from carious teeth, extensive phlegmon involving the face and retromandibular region of the neck, thrombophlebitis of the left jugular vein, metastatic abscesses in both lungs and the right kidney, with parenchymatous degeneration of the viscera. The pleurae showed numerous clumps of gram-positive cocci. No micro-organisms were found in the spleen. In the skin and lungs numerous staphylococci were seen. In the lower jaw gram-positive cocci were found in chains and in clumps as well as delicate gram-positive rods and gram-negative cocci and rods. The cervical glands contained staphylococci. Cultures from all of the organs yielded Staphylococcus pyogenes-aureus. Neurohistologic examination revealed; The meninges were swollen and showed a beginning meningitis; the blood vessels showed two types of lesions: (*a*) swelling of the intima and (*b*) distended walls, homogeneization and beginning necrosis of the nuclei. In some areas the distention

of the walls led to the formation of ball-like nodules. In others there was observed a perivascular lymphocytic and leukocytic exudate. The thalamus showed a small focus of infiltration with leukocytes and a small area bordering on necrosis. The ganglion cells showed three types of involvement: (*a*) severe degeneration; vacuolization of the cells in the cerebral cortex and in the striatum, with destruction and swelling of the Purkinje cells; (*b*) homogeneization and shrinkage of the cells and their nuclei in the olive and dentate nucleus, and (*c*) severe degeneration of the cells in the lateral horns of the spinal cord, with well preserved anterior horn cells and marked glial proliferation going on to the formation of glia nodules and neuronophagia.

KESCHNER, New York.

REPORT OF RESULTS FROM THE USE OF KETOGENIC DIET AND KETOGENIC DIET WITH WATER RESTRICTION IN A SERIES OF EPILEPTICS. G. J. DOOLITTLE, Psychiatric Quart. **5**:135 (Jan.); 225 (April) 1931.

In 1929, at the Craig Colony, a series of patients was placed on a ketogenic diet, and on a modified ketogenic diet with water restriction. The purpose of the investigation was primarily to ascertain how much the ketogenic diet and the modified ketogenic diet with water restriction would benefit institutional epileptic patients, and secondly, whether or not such treatment was practical from an institutional point of view and could be carried out satisfactorily with the personnel available in a state institution. Of 16 patients on the ketogenic diet, 11 had idiopathic epilepsy, and the other 5 showed some possible organic cause.

Sedation of every nature was first discontinued, and the number of attacks during this preliminary period were noted. At the expiration of five weeks, the following results were found: a total of 59 petit mal and 219 grand mal attacks and a weekly average of 11 petit mal and 44 grand mal attacks. All patients were given the regular Colony diet, and no attempt was made at water restriction. The patients were then placed on a strict ketogenic diet with a basis of carbohydrates, 6 to 10; protein, about 50, and fat, 150 to 200 calories, depending on the caloric need of the individual patient. The diets were made up chiefly of oranges, bacon, eggs, butter, lettuce, mayonnaise, crackers, olive oil, cheese and fat pork. No difficulty was experienced in changing from the ordinary to the ketogenic diet. There were no symptoms of nausea or vomiting. No distress occurred, such as has been mentioned by Barborka.

At first, the patients were elated over the diet; they ate well without urging. After about four weeks, many patients complained bitterly that the diet contained too much fat, and it became necessary to urge and watch them. The diet was continued for six weeks.

The urine was tested daily during the first four weeks. The test used was 10 per cent ferric chloride, and the reaction was graded as 1, 2 and 3 plus. The reactions were 2 or 3 plus in about 75 per cent of the cases, showing the presence of a fairly marked ketosis; the ketosis was marked in about 50 per cent and mild in 25 per cent. The percentages varied considerably from day to day. A daily record of weight showed a loss in some cases, ranging from 1 to 5 Kg. during the six weeks. One patient, however, gained 2.5 Kg. while on the diet; 2 others remained about the same. The majority of the loss of weight occurred relatively early in the treatment.

During the ketogenic period, 320 seizures occurred, divided as follows: 167 petit mal and 153 grand mal, as against 59 petit mal and 219 grand mal during the preliminary period of observation; the weekly average was 28 petit mal and 25 grand mal as against 11 petit mal and 44 grand mal.

After this, the patients were again placed on the regular diet and observed for four weeks with the following results: 255 seizures, 90 petit mal and 165 grand mal; a weekly average of 22 petit mal and 41 grand mal. Most striking is the alteration in the character of the seizures. The grand total of all seizures in the 16 cases during the period of observation was 278, against a grand total of 320 while on a ketogenic diet; but in 12 cases, or 75 per cent, there was a marked increase in

the total number of petit mal seizures during the diet, and in 13 cases, or 83 per cent, the grand mal seizures were decreased. In 3 cases there was an increase of grand mal seizures.

Of the patients showing improvement, 3 showed marked ketosis, 2 fairly well marked ketosis and 1 slight ketosis throughout the treatment. The greatest number of cases showing improvement came under the idiopathic type; in only 1 case with a possible organic origin was there improvement.

The duration of the epilepsy in these cases varied from six to twenty-eight years. In only 1 case was there a complete cessation of seizures during the period of diet. However, the duration of the epilepsy was fourteen and one-half years. The fact that the petit mal seizures increased about 73 per cent and the grand mal decreased almost 41 per cent would seem to indicate that this diet had a rather marked effect on convulsions, particularly as such a high percentage of the total number of cases showed this change from severe to mild seizures.

It has been found by the establishment of an Eck fistula in animals and a very stringent restriction of the protein given, that the animal will remain alive and in a healthy condition for a considerable period of time. However, if a large amount of protein, by the deamination that occurs in the tissues, upsets the normal blood reaction in such a manner that it becomes abnormally alkalinized, in other words, if the hydrogen ion concentration of the blood swings to the alkaline side, the animal goes into convulsions. It has long been thought that the liver is the only organ in which ammonia is converted into urea. If abnormal alkalinity of the blood is a causative factor of epilepsy, how much does an abnormality in the metabolism of protein influence seizures? It has been thought from a clinical point of view that such disturbances have an influence.

Another dietary restriction that has long been practiced, at least at the Craig Colony, is the limitation of gross sweets, such as candy, rich desserts, etc.; certain patients cannot tolerate these sweets in excess, and if they take them they experience an increase in the number of seizures.

Twenty-seven patients were placed on water restriction together with a ketogenic diet; all had cases of idiopathic epilepsy with one exception. All sedative treatment was discontinued prior to the experiment. After a preliminary fasting for twelve hours, the patients were given from 25 to 44 cc. of 40 per cent cream every four hours, without an intake of water; this meant a total of from 150 to 240 cc., of 40 per cent cream every twenty-four hours. This period lasted for forty hours. Following this, the patients were placed on a modified ketogenic diet and water was restricted to a degree depending on the amount of water each was in the habit of taking. Later, the diet was changed from a ketogenic to a strictly ketogenic diet, and the water was cut down still farther for a period of five days. Following this, nearly all patients showed an elevation of temperature. The weather became extremely hot, and it was necessary to increase the water intake slightly. The results were as follows: During the preliminary period of observation prior to water restriction, 337 petit mal and 582 grand mal seizures, averaging 67 petit mal and 116 grand mal per week, were recorded. It became necessary to discontinue with 2 patients owing to their inability to cooperate. When they returned to the regular Colony diet, they did not have an increase in the number of seizures. On water restriction there were 480 petit mal and 450 grand mal seizures, with a weekly average of 80 petit mal and 75 grand mal. Thus, the petit mal seizures increased 42 per cent, and the grand mal decreased 29 per cent.

The treatment was then discontinued, and the patients were observed for a period with the result that the petit mal seizures dropped to an average of 25 per cent per week and the grand mal rose to an average of 87 per cent.

The patients showed a loss of weight, chiefly during the first and second weeks of treatment. In 6 cases showing the greatest loss of weight, 3 patients showed improvement. Thus, 50 per cent of the patients showing the greatest loss of weight were improved. Three patients showed a marked increase in the number of seizures during the treatment. In 1 case in which a slight loss of weight occurred, slight improvement was shown. Mental improvement was marked in

2 of the 25 cases reported. One patient had almost treble the number of grand mal seizures under treatment, but showed a marked mental improvement. In 8 of 25 cases the patients seemed to show no tendency to water retention prior to treatment. In 5 cases the patients showed a tendency to excrete markedly less than they consumed, and of these patients only 4 showed improvement either mentally or as to seizures. Only a few of the patients seemed to show a tendency toward polyuria following seizures.

The specific gravity of the urine in these cases, taken daily, varied from 1.020 to 1.040, the average reading being from 1.029 to 1.036. In 1 case the patient showed symptoms of hyperthermia due to extensive dehydration. In the 25 cases reported, only 8 patients showed improvement, and they were all in the idiopathic group.

DOOLITTLE, Sonyea, N. Y.

CARBON MONOXIDE POISONING AND THE CENTRAL NERVOUS SYSTEM. E. POLLAK and P. REZEK, Arb. a. d. Neurol. Inst. a. d. Wien. Univ. **32**:95 (Oct.) 1930.

This contribution is based on five cases of carbon monoxide poisoning. In the first three cases, the patients were aged 4, 5 and 6 years, respectively. In none of these three cases did the pallidum show gross changes. The most striking histologic changes were observed in the striatum and adjacent internal capsule, whereas the pallidum showed only the earliest possible indications of perivascular necrosis. On the other hand, the striatum showed hemorrhages and coarse changes in the vessels. Especially prominent were the infiltrations of the vessels in this nucleus and in the adjacent internal capsule. Except for some very fine changes in the ganglion cells of the cerebral cortex and for small necroses in the spinal cord, there were no other pathologic alterations in the central nervous system. In contrast to these three cases, the fourth (in a patient aged 24) showed edema, lacunar spaces around the blood vessels, especially in the pallidum and white substance of the island of Reil, hemorrhages and some slight infiltrates. There were other changes in the parenchyma of the central nervous system, but these were insignificant.

The infiltrations in every case consisted only of monocytes. This is noteworthy in view of the fact that the patients were young and died while still exposed to the carbon monoxide gas or immediately thereafter. It would thus seem that infiltrations of the walls of the vessels may occur also in purely toxic states — a view that is now gaining more and more recognition. The occurrence of such reactions necessitates a revision of the usual conception of inflammation. It is becoming more and more apparent that the infiltrating components of pathologic tissue are not to be regarded as an expression of exudation, but that the infiltrating cells are part of a productive reaction of the vessel wall. They bear the same relationship to the other productive functions and formations of the elements of the vessel wall as the various mature forms of tumor cells bear to certain functional and germinal principles determining the various forms and types of cells in neoplastic formations. In other words, the infiltrating cells represent a less differentiated function than do the other proliferating elements of the vessel wall. They are morphologically least differentiated because their activity is restricted to the process of removal of the products of disintegration of tissue.

The intensity as well as the occurrence of such infiltrations is especially marked in younger persons, and it would seem that in older persons this type of reaction is very mild or does not occur. The infiltrate seems to be a transitory process which disappears very quickly, so that it may be regarded as an early manifestation of involvement of the brain in carbon monoxide poisoning.

If one compares the pathologic changes in the brains of children with those in the brains of adults, one finds that the chief differences are the occurrence of infiltrations in the walls of the blood vessels, hemorrhages and an intact perivascular tissue, and perivascular necrosis with only slight or no infiltrates in the blood vessels of the children. It would thus seem that in the adult, poisoning

with gas produces early degenerative changes in the perivascular tissue, with disturbance in the water content giving rise to edema and necrosis of the lacunar tissue. In view of all these facts it becomes obvious that early death from carbon monoxide poisoning reveals pathologic changes that differ greatly from those in patients who die late, and that the age of the patient determines the character of the morphologic process.

The fifth case occurred in a man, aged 60, who was exposed to carbon monoxide gas during the night of Oct. 23, 1917. When he regained consciousness the next afternoon, he was confused; during the next few days he suffered from sticking pains in both feet and weakness in the left hand. These symptoms persisted until August, 1918, when he showed a coarse bilateral tremor, active tendon reflexes in the upper extremities, which were more lively on the left, abdominal and cremasteric reflexes, a bilateral Lasègue sign, slight atrophy of the left thigh with moderate atrophy of the muscles of both legs, a flexion contracture of the right knee, both feet in an equinus position, with weakness more marked in the toes of the left foot, active knee jerks, absent ankle jerks and no signs of involvement of the pyramidal tract. Sensory examination revealed slight hypalgesia and hypesthesia in both lower extremities and slight disturbances in the deep sensibility of the toes. The patient also complained of occasional pains in both feet. Owing to the contractured knee joint, he was unable to walk. The clinical diagnosis was neuritis following carbon monoxide poisoning. The condition remained unchanged; death occurred from a severe hemoptysis on March 19, 1923. Necropsy revealed: subacute miliary tuberculosis, cheesy pneumonia of the upper lobe of the right lung with adhesive pleurisy, perforating aortic aneurysm (ascending position), subacute splenic tumor and parenchymatous degeneration of the viscera. Grossly, the brain appeared normal, but on frontal section an irregular cystic cavity, the size of a lentil, was found in the oval portion of each pallidum. The microscopic changes did not differ essentially from those generally described in cases of carbon monoxide poisoning in which death had occurred within a few weeks or months after the poisoning. The defect in the pallidum showed neither gliosis nor scarring of the connective tissue. A noteworthy observation was the presence of "abbau" processes of the same type as are observed during the earlier stages of the disease. It is difficult to say whether this was due to the persistence of an old process or to a new degenerative process. It is also difficult to estimate the rôle played by the diseased blood vessels in the affected area by failure of their normal function of removing the products of destruction of the tissue. Another significant observation was the presence of pseudocalcified deposits in the walls of the blood vessels. These changes also remind one of those observed in cases that do not terminate fatally until a few weeks or months after the poisoning. This, the authors believe, is confirmatory evidence that in this case the old process had been arrested, and that the changes in the walls of the vessels were due to the toxic effect of the gas, so that their permeability was diminished with a resulting retention of the poison, which in turn enhanced the colloidal binding of iron and calcium.

Aside from these changes, there were no striking neurohistologic changes that could be regarded as the primary effect of poisoning with carbon monoxide gas. The authors believe that the other changes are involutional; they are accidental concomitants that may be observed in any form of poisoning affecting the central nervous system. The only significant histologic change, then, is that in the pallidum. The specific structure of the blood vessels in the pallidum, especially of its oral portion, with the peculiar permeability of its walls is, according to Pollak and Rezek, the only factor at the basis of the most important component of the cerebral changes.

KESCHNER, New York.

CHIASMAL SYNDROME PRODUCED BY CHRONIC LOCAL ARACHNOIDITIS. W. M. CRAIG and W. I. LILLIE, Arch. Ophth. **5**:558 (April) 1931.

This article, if read in the original, should be so read after a paper on "Chronic Cisternal Arachnoiditis Producing Symptoms of Involvement of the Optic Nerves and Chiasm" (Heuer, G. J., and Vail, D. T.: *Arch. Ophth.* **5**:334 [March] 1931),

which also is reviewed in this number of the ARCHIVES. Both articles deal with the ocular syndrome produced by lesions at or near the optic chiasm.

In this paper, the classification of Cushing as it appeared in the *Archives of Ophthalmology* (**1**:168 [Feb.] 1929) is included: "(1) meningiomas with a parasellar rather than a suprasellar point of origin, (2) pituitary adenomas, (3) congenital tumors arising from the craniopharyngeal pouch, (4) gliomas arising from the chiasm or the third ventricle, (5) chronic local arachnoiditis, (6) syphilitic meningitis and (7) aneurysm." The authors stated: "Any one of these may affect the optic nerves, chiasm and either or both optic tracts in varied combinations, producing definite ophthalmologic changes as follows: (1) lowered central visual acuity; (2) pale optic disks, or simple optic atrophy; (3) bitemporal hemianopia for colors; (4) bilateral hemianopia for form and colors; (5) bitemporal scotomatous hemianopia for colors or form or for both; (6) temporal hemianopia with amaurosis of the opposite side; (7) temporal hemianopia with successive changes which lead to amaurosis, such as central scotomas, cecocentral scotoma, enlargement of the scotoma with islets of vision and of amaurosis; (8) homonymous hemianopic scotomas for form and colors; (9) homonymous hemianopia for colors, and (10) homonymous hemianopia for form and colors."

The authors call attention to a significant feature of the defects in the visual field produced by chiasmal lesions, i. e., the asymmetry of the defects, whether bitemporal or homonymous, in contrast to the symmetric defects produced by lesions affecting the optic tracts or the optic radiation.

The histories, the results of the clinical examinations and operations and the fields of vision in eight cases are presented; in three instances, necropsy reports are included. One of the patients, a man, aged 36, following an uneventful convalescence, continued to show evidence of diabetes insipidus by maintaining a high intake and output of fluid in spite of further treatment. After his return home, the condition remained stationary for a time, but he gradually declined, and died five months after the operation. The three cases in which necropsies were performed showed evidences of marked basilar meningitis or of localized cisternal arachnoiditis, with extensive adhesions around the optic chiasm.

The second section of the paper discusses the syndrome of Gowers-Paton-Kennedy, that is, optic atrophy with a scotoma on the side of the lesion and choked disk in the eye on the opposite side. The authors' experience shows that several combinations of signs in this, a basofrontal group of lesions, may arise: (1) a unilateral central scotoma with normal fundi; (2) a unilateral central scotoma with pallor of the disk, but normal conditions in the other eye; (3) bilateral central scotomas with pallor of both disks; (4) bilateral central scotomas with choked disks in both eyes; (5) unilateral amaurosis with simple optic atrophy, and choked disk in the opposite eye; (6) unilateral amaurosis with simple optic atrophy, and choked disk and central scotoma in the opposite eye; (7) central scotomas and various alterations of the peripheral fields due to secondary contraction resulting from choked disks, and (8) bilateral amaurosis with any of the foregoing changes in the fundus.

The eighth case presented illustrated these possibilities rather well. At operation, through a transfrontal approach, the right frontal lobe was elevated and the chiasm found to be covered with an exudate and bound down with adhesions. There was a definite exudate on the arachnoid over the right hemisphere. The space between the convolutions was filled with fluid which contained flocculent material, indicating that the right frontoparietal lobe was the seat of an inflammatory process; evidently, the process that had bound down the chiasm with adhesions also involved the base.

The authors' conclusions are: (*a*) chronic local arachnoiditis affecting the optic chiasm is a definite clinical entity; (*b*) the chiasmal syndrome from it is similar to that produced by a tumor in this region; (*c*) a definite preoperative diagnosis of the underlying lesion cannot always be predicated, and (*d*) operative results in this group justify surgical exploration.

SPAETH, Philadelphia.

IODINE DEFICIENCY AND GOITER: INFLUENCE OF A DIET POOR IN IODINE ON THE THYROID GLAND IN WHITE RATS. C. A. HELLWIG, Arch. Path. **11**:709 (May) 1931.

Chatin's theory that endemic goiter is the result of a deficiency of iodine is accepted by most American scientists. In mapping the areas of the United States in which goiter is prevalent, McClendon and Hathaway determined the iodine content of foodstuffs and water from goitrous and nongoitrous areas, and showed that there is little iodine in the vegetables and the waters of the parts of the United States in which simple goiter is a serious problem.

Marine and Lenhart, who studied extensively the effect of iodine on the mammalian thyroid gland, arrived at the conclusion that this gland undergoes hyperplasia whenever its iodine content falls below 0.1 per cent, and that the therapeutic effects of iodine are the result of restoring to the thyroid gland the normal amount of iodine.

A direct experimental proof for the theory of Chatin has never been attempted in this country. In southern Germany, Tanabe succeeded in producing hyperplasia of the thyroid gland by giving white rats a diet poor in iodine. Freiburg being situated, however, in a district where goiter is endemic, Tanabe's positive results must be regarded with great caution, since it is well known that in goitrous areas domesticated animals incur hyperplasia of the thyroid gland spontaneously. Tanabe's successful experiments must be repeated in a goiter-free country before they can be accepted as proof for the iodine-deficiency theory.

Wichita, Kan., is free from endemic goiter. There arises the question whether or not Tanabe's experiments would be positive also in this locality.

From the negative results of the author's attempt to produce goiter by means of an insufficiency of iodine in the food, inferences may be drawn that lack of iodine is neither the only nor the essential cause of endemic goiter. The positive results of the second experimental series with a diet rich in calcium indicate that a positive agent may not be a single specific factor, and this or these positive agents may not alone cause hypertrophy of the thyroid gland in the presence of a high amount of iodine in the food, nor may insufficiency of iodine in itself cause endemic goiter in the absence of the other agents that cause goiter, but when both are present, the conditions for the development of hyperplastic goiter seem to be at their optimum. Only by this conception of the etiology of goiter is one able to understand why endemic goiter may be present in localities rich in iodine, and, on the other hand, absent in regions poor in iodine.

The results of the last experimental series, in which hyperplastic goiter was produced with a diet rich in calcium and poor in iodine and in which colloid goiter was produced with a diet rich in calcium and iodine, are not in favor of McCarrison's theory that from an etiologic standpoint these two types of goiter are entirely different but indicate that the different structure of the thyroid gland depends on the amount of iodine in the food, the essential cause of the enlargement in each case being identical.

Comparative studies made in Europe following a suggestion of Aschoff have shown that the histologic structure of goiters varies according to the part of the country in which they occur. In certain regions, especially in level regions, the diffuse colloid goiter, with and without hyperthyroidism, and exophthalmic goiter predominate. In more mountainous countries the toxic goiter is an exception, and the nearer one aproaches the center of the endemic area the less one meets with the colloid goiter. It is replaced by the colloid-poor, diffuse, parenchymatous goiter in childhood and by the adenomatous, parenchymatous, nodular goiter with its degenerative forms in adults. It can hardly be doubted that, as is seen in the last experimental series, these differences in the architecture of the goiters are due to differences in the iodine content of the food, the positive etiologic factor, hitherto unknown, being the same and being world-wide.

WINKELMAN, Philadelphia.

THE CRIMINAL FEEBLEMINDED. F. C. RICHMOND, J. Am. Inst. Crim. Law & Criminol. **21**:537 (Feb.) 1931.

Richmond, who is director of the Wisconsin Psychiatric Field Service, states his belief that the public is either uninformed or misinformed concerning the prevalence and importance of the factor of mental deficiency as predisposing to delinquency and crime, and that only to a limited extent in New York and Massachusetts is the problem adequately dealt with by law. He asks a number of pertinent questions and draws attention to certain parallel aspects of mental disease and mental defect which provoke different reactions on the part of individuals and of organized society.

Any legal classification of the criminal feebleminded must of necessity be based on the statutes, and judicial opinions are cited with special reference to the statutes of Wisconsin. Consideration is then given to the adequacy of various psychiatric definitions and classifications of feeblemindedness and to the subject of mental testing or psychometry. The following definition is offered: "The criminal feebleminded are those persons under or within the jurisdiction of penal, reformatory or correctional agencies or institutions showing an intelligence quotient not above seventy-five, whose low mental level is due to arrested development."

The cause and incidence of feeblemindedness are discussed from the psychiatric standpoint, including new data covering examinations made in Wisconsin during the four year period from July 1, 1926 to June 30, 1930. From his data, Richmond draws the conclusion that the proportion of feebleminded among criminals and delinquents increases progressively as the age scale ascends, and that feeblemindedness is one of the outstanding factors, second only to broken homes, in the production of criminals and delinquents.

The following are selected quotations from volume 10 of "The Medical Department of the United States Army in the World War" to establish and confirm Richmond's stated belief: "Of the disciplinary cases reported by neuropsychiatrists, 42.3 per cent were mental defectives." "It was believed that no other class of men made for so much mischief in the Army as did the feebleminded." "There are sufficient grounds for excluding all mental defectives from the military forces except when the last available man power must be utilized." The question of legal responsibility of feebleminded persons for criminal acts is given extended consideration, and the present psychiatric trend in the direction of treatment and training, rather than of punishment, is stressed. Division of the criminal feebleminded is made into two classes: first, the potential delinquent, who requires protection, special training and supervision, and second, the confirmed or habitual delinquent, who requires segregation during which training, study and observation are combined with a view to returning to the community those who are selected as the most favorable risks.

Quotations from the literature are numerous and well selected; they include the modern program outlined in Davies' "Social Control of the Mentally Deficient," to which program the author adds the following: "The feebleminded inmates of penal, reformatory and correctional institutions serving sentences for felony shall prior to expiration of sentence be formally adjudged to be mentally deficient and as such committed to a proper institution. Those whose mentality is so deficient or whose delinquency is so chronic that their return to the community is contraindicated should be detained indeterminately, while those whose return to the community shall come to be considered practical would, following sterilization, be paroled indeterminately under the supervision of the law." In support of his final recommendation, Richmond states that mental deficiency, when not acquired, is transmissible from parent to child as a recessive characteristic made dominant by social selection obtained in mating.

WILLEY, Albion, N. Y.

HYPERTENSION IN RELATION TO THE BLOOD VESSELS OF THE MEDULLA OBLONGATA. C. R. TUTHILL, Arch. Path. **11**:760 (May) 1931.

In 1926, Bordley and Baker formulated the theory that hypertension was due to arteriosclerosis of the blood vessels of the medulla oblongata. The basis of this

theory was formed on the experiments of Anrep and Starling, who found that a decreased supply of blood to the brain causes an excitation of the vasomotor center, which results in a systemic increase of blood pressure. Bordley and Baker believed the location of the vasomotor center to be in the region of the obex. This conception was based on an investigation by Ranson and Billingsley, who showed in the cat that stimulation of the floor of the fourth ventricle seemed to locate the vasodepressor center lateral to the obex and the vasopressor center at the ala cinerea. Because of these experimental observations, Bordley and Baker studied the blood vessels of the medulla oblongata in the region of the obex. In their series, they found that in all the cases of prolonged hypertension there was arteriosclerosis of the blood vessels of the medulla oblongata, whereas in cases with a normal blood pressure, no arteriosclerosis of the vessels of this region was present. Cutler, in 1928, was unable to substantiate the claims of Bordley and Baker. He found that in some cases of hypertension, arteriosclerosis of the vessels of the medulla oblongata was not known. He also studied the vessels that supply the medulla, but could not find that in arteriosclerosis there were sufficient anatomic changes of the vessels to suggest a relationship to hypertension.

In the present study, the blood vessels of the medulla oblongata in the region of the obex were examined in twenty-four cases of hypertension and in thirty-five cases in which the blood pressure was normal. The cases of hypertension that were chosen occurred chiefly in older persons in whom the hypertension was of some duration. In order to compare the vessels in patients with hypertension with those in patients with a normal pressure, the medulla oblongata was studied in persons varying in age from 20 to 85.

In this report, arteriosclerosis is considered to be of three types. The first is arteriosclerosis of the large vessels, which is regarded as a connective tissue and elastic fiber hyperplasia of the intima with retrogressive changes. This is arteriosclerosis in the narrow sense, but in the broad sense two other types are included. The second is senile angiectasis, which is a laying down of connective tissue in all the walls of the blood vessels. The third is arteriosclerosis of the arterioles, which is considered to be a hyaline change taking place under the endothelium. Jakob, however, believed that this hyaline change of the arterioles of the central nervous system is found not only in arteriosclerosis, but in pellagra, syphilis, chronic intoxication and senility. Aside from the arteriosclerotic changes of the vessels, a reduplication of the elastic fibers was found in the endothelium in a few vessels. Such a reduplication was regarded by Jakob as an indication of syphilis, but since syphilis could not be demonstrated, the change was considered physiologic, owing to advancing age.

In twelve cases of hypertension, arteriosclerosis of the vessels of the medulla oblongata was found, but in the other twelve cases slight or no arteriosclerosis of these vessels was present. Among the cases of normal blood pressure, six showed arteriosclerosis of the vessels of the medulla oblongta. However, in none of the cases was arteriosclerosis confined solely to the vessels of the medulla oblongata. Therefore, in this histologic study of the vessels of this region, no proof is found that hypertension is the result of arteriosclerosis of the vessels of the medulla oblongata.

WINKELMAN, Philadelphia.

NEW FAMILIAL MALADY CHARACTERIZED BY A CONGENITAL CATARACT AND AN ARREST OF SOMATO-NEURO-PSYCHIC DEVELOPMENT. G. MARINESCO, S. DRAGANESCO and D. VASILIU, Encéphale **26**:97 (Feb.) 1931.

Case material is presented of a new type of congenital or familial condition that has not been described in the literature. Case 1, presented in considerable detail, shows: a bodily development giving the impression of a child aged 8 or 9 years, whereas the chronological age is 18; practically no evidences of pubertal changes; a certain degree of edematous infiltration of the skin; some rachitic deformations; bilateral cataract, and a slight horizontal instability of the eyes. The patient sits on the bed, with the head inclined, a picture of stereotyped immobility; walking is difficult; motor power is decreased, and hypotonia general.

Sensibility is normal. Mentally, the patient can carry out simple commands. The case may be summarized by saying that it is a retardation in somatic and neuropsychic development, accompanied by bilateral cataract, dating from the first year of life. Case 2, that of a brother, aged 17, is also presented in considerable detail. It is characterized by bilateral cataract, comparative immobility, poverty of spontaneous movement, inexpressive physiognomy and imbecility. Case 3, that of the third child, 8 years of age, shows the same type of arrest in somatopsychic evolution. In this case a biopsy of the right frontal lobe was performed. The architecture was normal and the layers were well developed. Chromatophil substance was diminished. Some of the cells in layer 3 were elongated, with the nucleus pushed nearer the periphery and with the dendrites unusually prominent. With Cajal stains, two kinds of cells were sharply differentiated, a clear and a dark type. The latter cells occupied almost the whole microscopic field. Microglia was without manifest alterations. With Scharlach stains a lipoidal disintegration was demonstrated in the basal part of the dendrites. The general histopathologic picture was one of a degeneration rather than an inflammation. Case 4, that of the fourth child, aged 4, is also included. In physical appearance and development she appears half this age; she cannot stand alone.

Wassermann tests give negative results in all, but in three of the children the reaction of Prunell, which some authorities consider as specific for hereditary syphilis, is positive. Estimations of blood calcium show: in the father, 7.76 mg.; in the mother, 10.99; in case 1, 8.53; in case 2, 6.9; in two normal children in the family, 9.2 and 6.7 mg. (normal from 10.5 to 12 mg.).

The authors summarize as follows: This is a familial condition, affecting several children in a family, characterized by the appearance of cataract, a retardation in somatic development, the presence of neuropsychic disturbance, and a hypocalcemia; one must admit that this last feature is constitutional because it is present even in brothers who are apparently sound, and in one parent. There are three possibilities of interpretation: a primary endocrine disturbance with secondary cerebral manifestations, an infantile encephalopathy with consecutive endocrine modifications, or a simultaneous disturbance of the nervous system and of the glands of internal secretion. Arguments for these various points of view are presented, with citations from the literature.

ANDERSON, Los Angeles.

NYSTAGMUS OF OCULAR ORIGIN. JAMES E. LEBENSOHN, Arch. Ophth. **5**:638 (April) 1931.

This article is an ophthalmologic review of the literature that discusses nystagmus of ocular origin. The outline classified by Fox which places nystagmus in five general groups is presented. Briefly, they are: nystagmus of vestibular origin, either physiologic or pathologic; of optic origin, here also either physiologic or pathologic; of neuromuscular origin, position or "Endstellungsnystagmus" and pathologic; of cerebellar origin, and last a group of cases with nystagmus of uncertain origin in which are included toxic states, cerebral lesions, disease of the higher cervical portion of the spinal cord and hysterical and voluntary nystagmus. It seems as if the last group overlaps, in part, all of the others, though, as stated, they are of uncertain etiology.

Ocular nystagmus, as the author points out, includes the nystagmus listed in the second and third divisions of the classification. The clinical characteristics of ocular nystagmus are discussed. The apparatus for inducing optokinetic nystagmus is illustrated.

It is of interest that the apparatus presented for inducing optokinetic nystagmus, designed by Shapiro and Pearlman, should have the same underlying principles as that of Brunner, which was presented in 1922 before the Vienna Academy of Medicine. If the reader desires to go further into this phenomenon of nystagmus of neuromuscular origin, Brunner's original article should be read with that of Shapiro and Pearlman, wherein they present their portable electric model for the development of "Endstellungsnystagmus."

The author points out, as did several earlier authors, the value of induced nystagmus from a diagnostic standpoint. Either inversion or reversion of a spontaneous nystagmus can be developed. Induced nystagmus is of importance in the diagnosis of paresis or paralysis of the ocular muscles; congenital fixation nystagmus; positional nystagmus; cerebellar lesions; lesions of Deiter's nucleus or of the labyrinthine nerve; lesions, as one author pointed out, situated near the posterior end of the sylvian fissure, i. e., the supramarginal gyrus and the gyrus angularis, and of the frontal lobe, especially when situated in the region of the motor area of the eye; lesions affecting the higher visual cortex and the nuclei of the oculomotor nerves, and lesions affecting the motor pathways to the nuclei of the ocular muscles.

Clinically, the author states that the test for optokinetic nystagmus should be of value in the following conditions: (1) to expose malingering in cases of assumed blindness; (2) to differentiate between nystagmus of vestibular origin and congenital fixation nystagmus; (3) to determine the existence of lesions in the optometer pathway, likewise to differentiate hemianopia due to lesions of the optic tract or optic radiation from hemianopia of cortical origin; only in the latter is there an absence of the quick phase on the hemianopic side; (4) possibly to stimulate paretic ocular muscles.

SPAETH, Philadelphia.

ANATOMIC CHANGES IN A CASE OF WESTPHAL-STRÜMPELL PSEUDOSCLEROSIS. W. KRYSPIN-EXNER, Jahrb. f. Psychiat. u. Neurol. **47**:251 (Dec. 11) 1930.

The clinical diagnosis in the case reported was: " dementia due to organic disease of the brain." The correct diagnosis was not established until the brain was subjected to histologic examination, although at necropsy the appearance of the liver pointed to a diagnosis of pseudosclerosis. The histologic examination of the brain revealed: Status spongiosus in the putamen, with nonspecific atrophy of the dentate nucleus and inferior olive. In the cerebellar cortex the Purkinje cells showed various types of degeneration, with proliferation of Bergmann's cellular layer and marked glial network formation. No typical Alzheimer cells were observed in the cerebellum. The ganglion cells in the pontile nuclei were not severely damaged and the glial proliferation was only moderate. Even on macroscopic examination, the atrophy of the brachium conjunctivae was striking, although the Nissl stain revealed nothing to account for this atrophy. In contrast to the severe changes in the frontal lobes, the cerebral cortex showed insignificant, nonspecific alterations in the cortex of the occipital and temporal lobes. In the frontal lobes the cortex was affected in all its layers. The changes in the cornu ammonis and in the gyrus hippocampi were also nonspecific and relatively slight.

Alzheimer's glia cells, generally accepted as characteristic of pseudosclerosis, were found in the pallidum and occasionally in other parts of the brain. Those in the pallidum were distributed in large areas and contained large pale nuclei without plasma and were surrounded by masses of green granules. It would seem that the pallidum has a special predilection for the formation of this type of cell. Large Alzheimer glia cells were also observed in the thalamus and substantia nigra, but the pigment was different in both of these structures. These cells were absolutely free from pigment when they were found in the cerebral cortex, except in the uppermost layers of the temporal cortex, where a few large glia nuclei with green pigment granules were seen.

Another peculiar type of cell found in this patient was one with pale protoplasm and a small nucleus. This type of cell was found throughout the entire brain, but only in areas in which ganglion cells were absent, namely, in the white matter of the internal capsule. Their appearance was entirely different from that of the Alzheimer giant cells, although some of them were surrounded by satellites and contained ameboid bodies ("gliophagia"). These cells are not specific for Westphal's pseudosclerosis. A cell similar in appearance had also been seen by the authors in the putamen in a case of cerebral syphilis with softening and by Jakob in a case of cerebral syphilis with stationary paralysis.

KESCHNER, New York.

CRITERIA OF RESPONSIBILITY. C. B. FARRAR, J. Am. Inst. Crim. Law & Criminol. **21**:438 (Nov.) 1930.

In this article, which was read by the director of the Toronto Psychiatric Hospital before the fifty-ninth annual congress of the American Prison Association at Toronto, Sept. 25, 1929, it is pointed out that psychiatry and criminology may each profitably partake of the experience of the other. The concept of responsibility is then developed, along with numerous interesting side lights, especially with reference to the legal responsibility of children. Responsibility may be ethical or legal, or the two values may coincide. The importance of changing customs, changing morals and changing laws is stressed with the quotation that "One can break six of the ten commandments and commit no crime." It may, then, be merely a matter of accident or of environment that determines whether certain men live out their lives as apparently law-abiding citizens, or pass to the ranks of the professional criminal.

In developing the psychiatric principle of dealing with the criminal as an individual, it is stated that not long ago persons called insane were dealt with much as were criminals and that the two classes were housed together. Psychiatry made the first departure toward the scientific method when it began to investigate as an individual personality the mental patient performing unaccountable acts. For the understanding of an individual, it is required that all the data that can be obtained from investigation, from examination and from prolonged observation shall be available. In securing these data the cooperation of the person being investigated is imperatively necessary. This is the rock on which psychiatry and criminal procedure generally parted company because of the reciprocal feeling of hostility between society and the criminal.

The concept of responsibility is then developed as an interrelationship between the individual and society, and some of the responsibilities of society to the individual are stated. The fact of conscious and unconscious motivation of conduct is discussed, and the problem becomes one of stimulus and response or of cause and effect. The idea of punishment is subordinated to that of prevention and treatment based on examination and study. Stress is laid on the principle that this does not lead to the judicial practice of discharge or acquittal because of irresponsibility, but to the legal utilization of social resources, such as investigation, supervision, probation and parole, which may be developed in the same way that extramural treatment of mental patients has been developed.

WILLEY, Albion, N. Y.

A NEUROLOGIC AND ETIOLOGIC STUDY ON ONE THOUSAND MENTAL DEFECTIVES. E. J. LARSEN, Acta psychiat. et neurol. **6**:37, 1931.

Larsen studied the history and present status of 1,000 mental defectives. He classifies his material as follows: A. Endogenous mental deficiency (762 cases): (1) mongolism, 63 cases; (2) myxedema, cretinism, 9 cases; (3) dysendocrine conditions not covered by (2), 15; (4) microcephaly, 28; (5) mental deficiency, in which there appears to be a hereditary disposition although there are no neurologic-somatic symptoms, 647 cases. B. Exogenous mental deficiency (238 cases): (1) hydrocephalus, 15; (2) organic cases, i. e., patients with neurologic symptoms that are not attributable to ordinary organic nervous diseases, 223 cases.

Among the mongolian idiots he found a number of exceptions to the classic dogmas—9 first born children, 2 only children, an instance of a mongolian idiot born of a mother only 23 years of age and an instance of 2 mongolian idiots in one family. The percentage of cases showing dysendocrinism (2.4) is lower than those reported by other authors (Szondi 33, Eisenberger 29). In 46.8 per cent of his cases of mental deficiency without associated neurologic somatic signs Larsen found a hereditary predisposition to mental deficiency. In contrast to this, the exogenous group showed this disposition in only 9.2 per cent. In this connection

he points out that certain mental defectives show progressive neurologic-somatic signs. This may be the result of a degenerative process that is progressive after birth, resulting in premature senility of the organism. The histories of some of the families in his cases seem to indicate a hereditary factor that is lethal to certain children—i. e., they are stillborn or die at birth—and sublethal to others—i. e., they show progressive neurologic-somatic degenerations. As an etiologic factor in mental deficiency, syphilis may be said to be of relatively slight importance. As an etiologic factor in the exogenous cases he discusses birth injury; 22.3 per cent of this group showed a history of a birth injury. In 14 cases the delivery was accomplished with forceps; in 12 the child was born prematurely; in 16 parturition was protracted; version and extraction were done in 4 cases; asphyxia was present in 15 cases; a solution of pituitary was employed in 2 cases, and in 4 cases the child was in such a bad condition immediately after birth that it was not expected to live. In contrast to this, birth injury occurred in only 4.9 per cent of the endogenous cases. The author points out that while birth injury is an important etiologic factor in mental deficiency, particularly in the more pronounced forms of the condition, it is not as important a cause as the hereditary predisposition.

PEARONS, Philadelphia.

CONGENITAL ANEURYSM OF THE BRAIN. HUGH REID, Brit. M. J. **1**:445 (March 14) 1931.

The clinical history and syndrome and the necropsy observations are given in the case of a woman, aged 33, who died of a ruptured congenital aneurysm at the base of the brain. The patient had been well until a month before death, when she had had a slight attack of vomiting and had complained of vague headaches. Vague symptoms persisted. Eight days before death, she fainted twice and vomited without warning. The following week, she had a low occipital headache and pain in the back, and felt feverish. Then suddenly she collapsed and became comatose. The muscles were flaccid, and all reflexes absent. The pupils were widely dilated. She died about seven hours later in coma.

At necropsy, a small saccular aneurysm, 1 by 0.05 by 0.05 cm., was found occupying the space between the two anterior cerebrals and springing from the junction of these arteries. It had ruptured on the lower side. There was an old fibrous clot which evidently represented the remains of an older hemorrhage.

The author gives the clinical symptoms of congenital aneurysm prior to rupture and those following rupture. Before rupture, localizing symptoms may be recognized from pressure on neighboring structures, dependent on the location of the aneurysm. For example, those of the anterior half of the circle of Willis may cause irritation of the second, third, fourth, fifth or sixth nerves. One reported case showed only trigeminal neuralgia. An irregularity of the pupil on one side may be the only sign. In the posterior half of the circle of Willis, pressure on the brain stem, in addition to paralysis of the last four cranial nerves, might give rise to paraplegia, cerebellar symptoms, dysarthria, dysphagia or contralateral hemianesthesia.

After rupture, leakage of blood into the subarachnoid space at the base of the brain produces clinical signs on which a diagnosis may be made with reasonable certainty. The author adds, however, that in some cases meningitis or influenza may be closely simulated. The symptoms are dependent on the rate of the hemorrhage. Loss of consciousness passes on to deep coma with a severe hemorrhage, while with a small one, giddiness, headache and vomiting may be the only effects. Moderate pyrexia, stiffness of the neck and a positive Kernig sign may be present. In these latter cases, a differential diagnosis from meningitis is made by an examination of the cerebrospinal fluid and the suddenness of onset.

FERGUSON, Niagara Falls, N. Y.

EMBOLISM AND THROMBOSIS; PROLONGED DIRECT OBSERVATION OF THE PHENOMENA IN PIAL VESSELS OF THE LIVING CAT. A. W. ARMENTROUT, Arch. Path. **11**:519 (April) 1931.

The present status of knowledge concerning embolism and thrombosis has been attained through clinical examinations, autopsies, experiments on animals and observations made directly on the streaming blood. The original object in this investigation was the study by direct observation in the living animal, of the effects produced by fat emboli, in the pial blood vessels, and the comparison of these effects with those produced by various other foreign-body emboli. The results are perhaps more significant from the point of view of the fundamental problems of embolism and thrombosis.

Following embolism in the cat, the first reaction that occurs is the separation of the foreign body, no matter what its nature, from the blood stream by a collection of platelets, a "white thrombus," which is extremely friable and breaks off easily. The formation of this thrombus practically ceases when separation of the foreign body from the blood stream has been accomplished. If the endothelium has been injured by the foreign body, progressive thrombosis occurs. The distinction between these two processes probably lies in the freeing of thromboplastic substances in the latter instance. When progressive thrombosis does not occur, the external surface of the white thrombus is apparently entirely bland, so that the blood continues for many hours to flow past the obstruction, even when the space between the embolus and the opposite vascular wall barely admits a single erythrocyte. The effect of slowing of the blood current on this process, namely, the exteriorization of foreign bodies from the active blood current, is not perceptible. If not originally large enough to occlude the blood vessel, in general, the white thrombus does not grow large enough to do so, even in the presence of a failing blood stream or when bathed in blood that flows only intermittently. This last observation is contrary to all previously reported opinions.

In the pia, no perivascular reaction to vascular occlusion can be observed.

WINKELMAN, Philadelphia.

HEMIANOPIC MACULAR SCOTOMA WITH HEMIACHROMATOPSIA. PAUL PESME, Rev. d'oto-neuro-opht. **9**:13 (Jan.) 1931.

A retired officer, aged 69, complained that for the preceding fifteen days he had been unable to read. After correction of a hypermetropic astigmatism, the visual acuity was 9/10 in the right and 8/10 in the left eye; the eyegrounds were normal. Still the patient declared he could not read; he could see one letter after another but not together. The visual fields for white showed no change. Further tests revealed a right lateral homonymous hemianopic scotoma in the macular region, cutting the central fixation point by a vertical straight line. There was also abolition of the color sense in the right lateral half of the field. The only other complaint was a left temporal headache, which began at the same time as the inability to read. A general examination revealed a marked arteriosclerosis.

Since it was believed that the origin of the visual difficulty was a circulatory disturbance in the left cuneus, pancreatic extract was given, and in a month the scotoma disappeared.

Macular hemianopic scotomas are rare. The hemianopias usually seen cause partial or complete blindness of a half of the visual field with conservation of the macular field, but in this case the macular field was involved. The association of a hemiachromatopsia points to a lesion affecting the optic radiations or their cortical terminations in the point of the cuneus, which is an extremely vascular region. The transient nature of the scotoma was due to an ischemia from angiospasm.

A curious feature is the patient's unconsciousness of the cause of his trouble. This is the rule in such cases. However, Souques and Odier saw a case of macular hemianopic scotoma of traumatic origin in which the patient recognized the nature of his visual disturbance. Perhaps in hemianopias from traumatism this factor is

less marked than in those from softening. In the latter there is a constant, more or less marked word blindness.

DENNIS, Colorado Springs, Colo.

BIOLOGICAL AND SEROLOGICAL METHODS IN THE DIAGNOSIS OF EPILEPSY. J. THURZO, J. Neurol. & Psychopath. **11**:36 (July) 1930.

The author reviews all of the different tests of precision in the diagnosis of neurologic disease and their relationships to epilepsy. He finds that several tests are suggestive, but none conclusive. However, there are two examinations that gave him strongly suggestive results.

His entire thought and research are based on the toxic causation of epilepsy. He reviews the literature and shows that, from certain reports, the cerebrospinal fluid has certain chemical variations from the normal. These reports show the presence of choline, an increase in urea content and a decrease in albumin content in the spinal fluid. The author also points out that inoculation of rabbits with blood and spinal fluid of epileptic patients caused convulsions. But an absolutely negative spinal fluid spectrum has always been observed; in other words, nothing characteristic has ever been proved.

However, colloid reactions may be regarded as the most precise among all tests for epilepsy. And of all the colloid tests the most useful is the China ink test. Its simplicity recommends it, as well as its apparent accuracy. The claim is made that the test is positive in 87 per cent of cases of epilepsy. The test is a simple precipitation test, with three dilutions. The colloid protecting index is 0 in normal cases; i. e., precipitation in the first two tubes and none in the third, while in epilepsy the results show a colloid precipitation index of 2.

ROBINSON, Kansas City, Mo.

STUDIES ON AMPHIBIAN METAMORPHOSIS: VII. THE INFLUENCE OF THE COLUMELLA ON THE FORMATION OF THE LAMINA PROPRIA OF THE TYMPANIC MEMBRANE. O. M. HELFF, J. Exper. Zool. **59**:179 (Feb. 5) 1931.

A central area of the lamina propria of the anuran tympanic membrane directly over the tip of the columella becomes considerably thickened and is characterized by yellow, elastic, fibrous elements in its development during metamorphosis. The columella of *Rana pipiens* was extirpated during early stages of development, and the tympanic membranes were removed and examined histologically following metamorphosis. No traces of a thickened yellow fibrous area could be found in the lamina propria of the membranes. Columellae in various stages of development were extirpated and transplanted autoplastically beneath the pigmented membranous covering of the back musculature. In several cases typical yellow fibrous areas developed in the membrane directly over the end of the transplant. Annular tympanic cartilages, in fairly well developed stages, were extirpated; the attached columellae were removed, and the cartilages were then transplanted autoplastically, together with their lateral covering of lamina propria, to the back. During metamorphosis, typical tympanic membranes formed in the back integument, which, however, lacked the thickened yellow fibrous region. The results indicate that normal development of the yellow fibrous region of the lamina propria is brought about by association and contact of the membrane with the distal end of the rapidly growing columella.

WYMAN, Boston.

ENCEPHALOGRAPHIC STUDIES IN GENERAL PARESIS. FRANKLIN G. EBAUGH, HENRY H. DIXON, HUGH E. KIENE and KENNETH D. ALLEN, Am. J. Psychiat. **10**:737 (March) 1931.

Encephalograms were taken in the cases of seventy patients with dementia paralytica. The procedure was safe, and was tolerated with less distress by these patients than is usual among normal persons. The Colorado group uses a two-needle method, with the patient in the erect sitting posture. A small Bucky

diaphragm was used for the roentgenograms at a distance of 50 inches (127 cm.). The time of exposure in each case was four seconds. Views were taken from various angles, but the anteroposterior pictures were always distorted by the shadows of the frontal sinuses. In many patients with dementia paralytica Ebaugh and his colleagues found obliteration of the cortical pathways of the cerebrospinal fluid, especially in the frontal and parietal areas, owing, apparently, to a damming up of the fluid over these areas of the cortex — this is the so-called "arachnitis pattern." In the deteriorated patients, x-rays often revealed large areas of cortical atrophy. After malaria treatment, many of the "arachnitis patterns" were no longer seen, suggesting that in some way fever therapy relieves obstruction and allows full drainage with fluid release. With further development in the technic of taking and interpreting encephalograms, Ebaugh hopes that this may become a valuable method of assigning a prognosis and gaging the efficacy of treatment.

DAVIDSON, Newark, N. J.

NIEMANN-PICK'S DISEASE WITH CHERRY-RED SPOTS IN THE MACULA. ISADORE GOLDSTEIN and DAVID WEXLER, Arch. Ophth. **5**:704 (May) 1931.

This paper is a discussion of the microscopic pathology of Niemann-Pick's disease. The microscopic material was obtained from a Jewish girl, aged 10 months, who died following a period of intermittent fever and of sepsis five months after admission to the hospital. The article abstracts the literature on this pathologic process and summarizes it briefly. The important points connected with it are: (1) degeneration of the ganglion cell layer of the retina, corresponding closely to that described in Tay-Sachs' disease; (2) vacuolation of the cells of the nuclear layers, causing a striking honeycombed appearance; (3) the presence of pigmented, vacuolated cells in the choroid; (4) the presence of vacuolated histocytes about the scleral vessels and in the episclera, and an infiltration of these cells among the fibers of the sclera, and (5) a group of ganglion cells in the episclera, in intimate contact with the ciliary nerves, exhibiting changes similar to those of the cells of the brain and of the ganglion cells elsewhere in this case; a granular degeneration of Nissl's substance, with swelling of the cell and vacuolation of the cytoplasm.

SPAETH, Philadelphia.

THE GROWTH OF EYES AND LIMBS TRANSPLANTED HETEROPLASTICALLY BETWEEN TWO SPECIES OF AMBLYSTOMA. VICTOR C. TWITTY and JOSEPH L. SCHWIND, J. Exper. Zool. **59**:61 (Feb. 5) 1931.

Eyes and limbs were grafted heteroplastically between embryos of Amblystoma punctatum and the larger Amblystoma tigrinum, and their subsequent growth was compared with that of the undisturbed organs on the donor species. Feeding was standardized by offering the animals all the food that they would voluntarily consume. Eyes and limbs transplanted between embryos of these forms showed the same growth rate as their normal control organs on the donor species, although differing greatly in size from the normal organs of the host. Preceding metamorphosis, the two organs on the tigrinum became slightly larger than the corresponding organs on the smaller punctatum larva. This difference was so small that its significance is doubtful. The experiments show that the difference in size between the transplanted organ and the normal organ of the host species is due to differences in intrinsic growth factors. The close correspondence in size of the transplanted organ and its control on the donor species suggests a similarity in the organic environmental factors regulating the growth of the organs in the two forms.

WYMAN, Boston.

THE NECESSITY FOR CENTRAL REGISTRATION OF MENTAL DEFECTIVES. NEIL A. DAYTON, Ment. Hyg. **15**:364 (April) 1931.

The radical changes in the social and economic habits of the country call attention to the mentally deficient, who, if not more numerous than before, are

more conspicuous. Although statistics indicate that only 100,000 feebleminded persons are being cared for, there are, Dayton believes, 5,000,000 mentally deficient persons in the United States. To meet the problem in an honest manner, one must have adequate records of the distribution of these feebleminded persons, and must possess information about their heredity, their environment and the extent of the deficiency. Only seven states have a central bureau of registration for this purpose; their sources of information include the data of the public school clinic and the special class, the lists of patients in and awaiting admission to institutions for the feebleminded, the records of neuropsychiatric dispensaries and of child-guidance and habit clinics, the data of correctional institutions, juvenile courts and social agencies, and reports of psychometric studies in hospitals for mental diseases, prisons and other state agencies. These various sources of information should be coordinated; data should be obtained in a standardized manner, and a central bureau for the registration of mentally deficient persons should be established.

DAVIDSON, Newark, N. J.

PATHOLOGY OF THE GANGLION CELLS IN MULTIPLE SCLEROSIS. G. ZELLMANN, Arb. a. d. neurol. Inst. a. d. Wien. Univ. **32**:121 (Oct.) 1930.

The spinal cords in six cases of multiple sclerosis, varying as to the age of the patients and the duration of the illness, were studied histopathologically. There was no loss in the number of ganglion cells, but they showed three characteristic types of degeneration regardless of the age of the patient or of the duration of the disease: (1) swelling of the cells and their prolongations, with tigrolysis; (2) atrophy, with curling up of the dendrites and clumping of the tigroid substance, and (3) fatty degeneration, which was very marked in every case. All cells showed a characteristic fibrillolysis. It was impossible to ascertain definitely whether the swelling of the cells was not an early stage of atrophy or shrinkage, although it was evident that the swelling assumed the characteristics of axonal degeneration. This, therefore, confirms the present, generally accepted theory that in this disease the axis cylinders may also be destroyed. The sections showed furthermore that the destruction of the cells in the affected segments occurred in groups, and that multiple sclerosis produces not only insular foci in the white substance but also disseminated areas of degenerated cells in the gray substance.

KESCHNER, New York.

A MEDICAL PROBLEM THAT BECAME A PSYCHOLOGICAL PROBLEM. LOUISE NELSON, Ment. Hyg. **15**:242 (April) 1931.

A boy, aged 19, was referred to a psychologic laboratory because he had great difficulty in reading; he had never finished reading a book and did not even read the newspapers. Psychometric study showed that he had normal intelligence, and a physical examination gave negative results, excepting for a high degree of myopic astigmatism with congenital retinal defects in one eye. The psychologists were successful in drilling the patient in reading; at first they accompanied the reading by tracing the letters, as the boy seemed "motor-minded." After four months, he showed definite improvement, and even undertook to borrow books from the library. He never finished reading any of the books he borrowed, however. He was soon lost sight of. Nelson believes that this boy found difficulty in reading when he was a child because of the ocular defect, and that as a result he found this process associated somehow with an inadequate emotional life, until poor reading had become a habit and poor eyesight an excuse. Had this error in vision been discovered in earlier life and had it been properly corrected then, the boy, Nelson thinks, would have had a much more satisfactory emotional life. This patient was never examined neurologically.

DAVIDSON, Newark, N. J.

CLINICAL VALUE OF A NEW REFLEX IN CHOREA. G. A. STEPHENS, Brit. M. J. **1**:303 (Feb. 21) 1931.

The author finds what he calls the dorsal reflex in most choreic patients. There is hypersensitiveness on both sides of the spine, usually from about the third dorsal level and extending down to the buttocks; when the skin in this region is picked or scratched there is contraction of the underlying muscles. The author does not find this reflex in patients suffering from acute rheumatism and acute carditis. He is of the opinion that chorea really represents a toxemia, primarily dependent on calcium deficiency. Physiologic changes dependent on altered calcium metabolism affect primarily the vascular system, causing a diminished supply of blood to the muscles and vital organs and thus producing the mental changes and the choreic effect on the muscles. In his opinion, chorea is a sort of Raynaud's disease or "spasm" of the arteries of the brain. Thus, in regard to the "choreic reflex," the author believes that it suggests some interference with the blood supply to the afferent parts of the nervous system, especially in the neighborhood of the midbrain, and concludes: "The fact that I have seen this dorsal reflex in a case of encephalitis tends to support my doctrine." The essential aspect of the therapy advised is the administration of calcium lactate and parathyroid extract.

FERGUSON, Niagara Falls, N. Y.

THE CAUSE OF DEATH IN MULTIPLE SCLEROSIS. M. ZELLMANN, Arb. a. d. neurol. Inst. a. d. Wien. Univ. **32**:129 (Oct.) 1930.

This paper is based on a study of fifty cases of multiple sclerosis in the Wiener städtisches Versorgungshaus. The most common cause of death among these patients was pneumonia (58 per cent); the next, sepsis in the form of gangrenous decubitus, cystopyelitis, purulent hemorrhagic cystopyelitis, purulent leptomeningitis, peritonitis and renal abscess (36 per cent), and the third most common cause was stenocardia (6 per cent). Most male patients died from pneumonia and most female patients from sepsis. Pneumonia killed persons in the fourth, fifth and sixth decades of life, while sepsis was the cause of death during the third and fourth decades of life. None of the patients died as a result of the multiple sclerosis. The author also points out that in the female patients, the sepsis usually began near the anal and vaginal orifices as a result of sphincteric disturbance with secondary bed sores. The problem of prophylaxis may, therefore, be said to be one of prevention of infections.

KESCHNER, New York.

HUNTINGTON'S CHOREA. CHARLES STONE, Ment. Hyg. **15**:350 (April) 1931.

Since the movements represent only a single feature of hereditary chorea, Stone suggests that the condition be designated "Huntington's syndrome." The disease is an abiotrophy, with necrosis of the ganglion cells of the caudate and lentiform nuclei; the small cells are especially affected with fibrous gliosis and scar formation. The cortex, particularly the precentral and frontal areas, is consistently involved. Heredity is continuous, and if the members of one generation present no symptoms, the thread seems broken, for succeeding generations are free. The onset is usually between the ages of 30 and 40, with mental symptoms such as anger, absent-mindedness and defects in judgment, perception and memory, which manifest themselves early. The sudden movements of flexion and extension of the extremities and grimacings of the face occur at an irregular rate, about 80 per minute. Diagnosis is based on the sudden, purposeless, choreiform movements, the gradual progress of symptoms, the mental changes, the late onset and a hereditary history. In demonstration of this, Stone presents a family that had five cases of Huntington's syndrome in four generations. There is no effective treatment.

DAVIDSON, Newark, N. J.

A Case of Pituitary Tumour. C. C. Elliott and D. P. Marais, Brit. M. J. **1**:297 (Feb. 21) 1931.

The authors report a case of pituitary tumor, verified by operation and removed successfully, which was followed for a period of six years. The peculiar and unusual mental symptoms constitute the chief interest in this respect. The patient, a professional man, was observed by his partner to be falling behind in his work. He spent most of his time writing voluminously behind closed doors, and usually at the end of the day destroyed the products of his labor. From several letters that were not destroyed it was discovered that he was writing fantastic, bizarre day-dreams, resembling the grandiose, expansive delusions of the psychotic patient with dementia paralytica. In conversation, intelligence and other conduct he was his normal self. Other symptoms, including the results of a perimetric examination, pointed to a pituitary tumor. Following removal of the tumor, the strange fantasies persisted but with some improvement during the next six years. They were usually most intense at the end of the day or when the patient was fatigued.

Ferguson, Niagara Falls, N. Y.

Does Climate Affect the Human Conception Rate? C. A. Mills and F. A. Senior, Arch. Int. Med. **46**:921 (Dec.) 1930.

By considering the birth rate for any month and counting back forty weeks, Mills and Senior established the rate of conception for the earlier month. These rates were then plotted on charts and compared with the humidity and temperature for the same period. In northern cities, such as Montreal, the rate of conception was highest in June and lowest in January; in most of the United States, however, the rate of conception fell during the summer, and in the cities of the South this depression was marked. The graphs demonstrated that conception was most frequent when the temperature approximated 65 F. That this might be due to infrequency of sexual intercourse during hot weather is denied by Mills and Senior, who cite statistics pointing to a seasonal constancy in the use of houses of prostitution; these figures, however, were obtained from Japan. Their conclusion is that hot weather actually reduces fertility, and that there are significant seasonal changes in the rate of conception in human beings.

The Physiogenic and Psychogenic in Schizophrenia. Eugen P. Bleuler, Am. J. Psychiat. **10**:203 (Sept.) 1930.

Schizophrenia, Bleuler believes, rests on a physical basis, but its specific symptomatology is psychically determined. He suggests that there is sufficient disease in the brain to indicate a lesion which is presumably the anatomic substratum of dementia praecox, while the precipitation of the psychosis out of the environment is psychogenic. Thus, a person who already has the organic stigmas of schizophrenia may find himself failing in business; rather than believe he is at fault, he will assign his failure to the enmity of others and as this delusion progresses he will rationalize by means of hallucinatory evidence. In this way the disease is developed as a result of a psychic reaction to environmental difficulties, yet it rests primarily on organic defect. Bleuler also believes that complete prognostic pessimism is unjustified, that improvement and even recovery will occur in more cases than might be expected and that the outlook can be measurably improved by intelligent treatment.

Gumma of the Brain. R. D'Aunoy, A. Friedrichs and A. Zoeller, Am. J. Syph. **14**:175 (April) 1930.

Although syphilis of the central nervous system is common, cerebral gumma is rare. The condition is found in the later stages of syphilis and symptomatically is like a tumor of the brain. Even the serologic studies are uninformative; in the case presented the Wassermann reaction of the spinal fluid was negative.

Gummas localize like meningiomas, and are most often found in the meninges along the convexity of the brain. The authors call attention to the fact that modern opinion is turning from the idea that these growths respond well to iodides and mercury, and he quotes Solomon, Schlesinger and Friedlander in support of his belief that medical treatment is unsatisfactory. Surgical measures are recommended, the suggestion being that decompression should be performed first, and removal of the growth be undertaken when this seems practical. Specific treatment should accompany and follow these procedures.

THE ASSOCIATION OF RAYNAUD'S DISEASE WITH CEREBRAL SYMPTOMS. LOUIS CARP, Arch. Surg. **22**:409 (March) 1931.

The cerebral symptoms of Raynaud's disease are more frequent than is commonly thought; these symptoms are usually in the form of convulsions, headache, vertigo, or paralysis. Carp reports a case in which cerebral symptoms preceded by three years the peripheral manifestations of Raynaud's disease. His patient, a young man, had been complaining of headaches on the right side, poor vision in the right eye, and a feeling of general depression. Pain, blueness, and coldness in the right index finger rapidly developed, and one morning there was a sudden vascular accident in the right side of the brain, which left him with a left hemiplegia. During the period of this paralysis the radial and brachial arteries on the right side were hard and pulseless. The patient died, and a postmortem examination was not obtained.

APPARENT SPECIFIC EFFECTS OF SODIUM IODIDE IN HERPES ZOSTER. E. WOOD RUGGLES, Arch. Dermat. & Syph. **23**:472 (March) 1931.

Using 2 Gm. of sodium iodide intravenously, Ruggles was able to bring about relief from pain and disappearance of the vesicles in cases of herpes zoster. Fifteen cases are reported and in every one the skin was normal in less than three weeks; in some of the cases, complete relief was afforded within ten days. Three or four injections are usually given. Ruggles advises giving sodium iodide on the first day and again on the second; no injection should be given on the third day; the drug should again be introduced intravenously on the fourth day. If a fourth injection is necessary, this should be given on the seventh day. In an earlier issue of the same journal (ARCH. DERMAT & SYPH. **22**:101 [July] 1930), Sidlick reported that hypodermic injection of 1 cc. of solution of pituitary would cause disappearance of herpes zoster.

DAVIDSON, Newark, N. J.

THE INCREASE OF NON-PROTEIN NITROGEN AND THE DECREASE OF CHLORIDES IN THE BLOOD FOLLOWING THE VOMITING OF GASTRIC CRISES. OLIVE CHRISTENSEN, Acta psychiat. et neurol. **6**:5, 1931.

The author studied the amount of nonprotein nitrogen and the amount of chlorides in the blood of three patients with gastric crises. Nonprotein nitrogen increased as the vomiting became more violent and decreased as it lessened, while the chlorides behaved in the opposite manner. From his study of the literature and his observations he believes that all patients with pernicious vomiting should be treated by the rectal, intravenous or subcutaneous administration of large amounts of chlorides.

PEARSON, Philadelphia.

KETOSIS IN SEA-SICKNESS. J. R. MARRACK, Brit. M. J. **1**:178 (Jan. 31) 1931.

The relationship between ketosis and acidosis and sea-sickness is evaluated. The author was able to show that ketosis is usual in sea-sickness after vomiting has begun. Occasionally it may appear earlier. In his opinion it is not a cause either of the disturbance itself or of any of the symptoms of sea-sickness. The

author believes that there is no evidence to indicate that acidosis will produce vomiting or any symptoms other than hyperpnea. In fact, he says that the symptoms of sea-sickness are more suggestive of the collapse seen from alkalosis. He does not indicate the number of cases comprising his series.

FERGUSON, Niagara Falls, N. Y.

MECHANISM OF SOME CONVULSIVE MOVEMENTS OF THE ORBICULARIS AND OF THE FACE. TOM A. WILLIAMS, Arch. Ophth. **5**:272 (Feb.) 1931.

This article is a discussion and presentation of cases in which certain convulsive movements of the orbicularis and of the face occur. The manner and method of their removal are also discussed. Tics, their etiology and treatment are old problems for the neurologist. They illustrate merely that convulsive movements depend on psychologic mechanisms found when the movements have as a basis some physical defect or psychologic point of irritation. Both may be present, but in some instances only the former seems to be the cause.

SPAETH, Philadelphia.

RESEARCHES ON INTESTINAL WORMS AS AN ETIOLOGIC FACTOR IN MULTIPLE SCLEROSIS. KNUD H. KRABBE and OLINE CHRISTENSEN, Acta psychiat. et neurol. **5**:509, 1930.

The fact that pernicious anemia and its associated myelopathies may result from toxins produced by intestinal parasites led the authors to study nineteen cases of multiple sclerosis for evidences of intestinal infestation. The stools of each patient were examined on three occasions, but in no instance was any intestinal parasite found.

PEARSON, Philadelphia.

CEREBROSPINAL RHINORRHEA. FRANK A. PLUM, Arch. Otolaryng. **13**:84 (Jan.) 1931.

A case of rhinorrhea that had existed for eighteen years is reported. The discharge was intermittent in a case in which there was probably an ingrowth of nasal mucous membrane through the floor of the anterior fossa. Falls in childhood may have had a bearing on the condition, although the rhinorrhea did not follow immediately. The case was complicated by frontal sinusitis and several intranasal operations.

HUNTER, Philadelphia.

THE ACTION OF CERTAIN AUTONOMIC DRUGS UPON THE PIGMENTARY RESPONSES OF FUNDULUS. DIETRICH C. SMITH, J. Exper. Zool. **58**:423 (Jan. 5) 1931.

The effects of certain sympathetic and parasympathetic stimulants and depressants on the dermal melanophores of *Fundulus heteroclitus* were studied. Solutions of the drugs were injected into the body cavity. Cocaine, ergot, pilocarpine, physostigmine and atropine were used. On the basis of the experiments the author concludes that the melanophores of fishes probably possess a double, rather than a single, innervation.

WYMAN, Boston.

UNILATERAL EXOPHTHALMOS FOLLOWING ADMINISTRATION OF THYROID EXTRACT. T. G. MOORHEAD, Brit. M. J. **1**:442 (March 14) 1931.

A case is reported of unilateral exophthalmos developing in a patient, aged 54, who had previously suffered from myxedema for which the administration of 12½ grains (0.812 Gm.) of thyroid extract had been given daily for about a year. Although in this case no thyroid tissue could be palpated, the patient had symptoms typical of thyroid intoxication.

FERGUSON, Niagara Falls, N. Y.

NUCLEAR CHANGES SIMULATING INCLUSION BODIES IN DORSAL-ROOT GANGLION CELLS. H. A. DAVENPORT, S. W. RANSON and E. H. TERWILLIGER, Anat. Rec. **48**:253 (Feb. 25) 1931.

The phenomenon of nuclear changes resulting from soaking in a hypertonic solution of sodium chloride prior to fixation suggests that the nuclear inclusions observed pathologically may be the result of disturbed osmotic conditions in the cell.

COBB, Boston.

Society Transactions

LOS ANGELES SOCIETY OF NEUROLOGY AND PSYCHIATRY

Regular Meeting, Jan. 28, 1931

I. Leon Meyers, M.D., *President, in the Chair*

The Rôle of Dysinsulinism in the Epilepsy Syndrome. Dr. J. M. Nielsen.

The term dysinsulinism, originated by Seale Harris (*J. A. M. A.* **83**:720, 1924), has gradually come into use to denote a clinical condition characterized by attacks of unusual hunger, dizziness, tremor, faintness and even coma and convulsions which is thought to be due to a disordered function of the islands of Langerhans of the pancreas. The term hyperinsulinism was first applied to the syndrome, but it was soon found that the blood sugar might at times be abnormally high as well as abnormally low in patients with this syndrome. No symptoms other than the actual finding of an excess of dextrose in the blood have been observed that would indicate clinically that the elevation of blood sugar occurs, but the symptoms listed would indicate that hypoglycemia is present.

Hypoglycemia may, however, be due to disturbance of the pituitary, thyroid, liver or suprarenals as well as to that of the pancreas. Omitting from this discussion pituitary and thyroid disturbances which are recognized with relative ease, I shall indicate briefly the factors relative to the other glands concerned in the maintenance of the blood dextrose level.

The liver has the function, among others, of storing glycogen, which it prepares from excess of dextrose in the blood. This action is stimulated by insulin, and of course tends to lower the blood sugar level. Insulin also accelerates the production of dextrose from glycogen by the action of epinephrine on the liver. Hyperadrenalinism therefore increases the blood sugar, and a hypofunction of the suprarenals causes hypoglycemia.

Furthermore, it has been shown (Nielsen: *J. Nerv. & Ment. Dis.* **63**:456, 1926) that hypoglycemia is an almost constant occurrence in generalized vagotonia. This is in entire agreement with the preceding remarks, inasmuch as vagotonia means a relative hypofunction of the sympathetic system and of the suprarenals.

From all this it is evident that the clinical syndrome of hyperinsulinism might, with equal propriety, be called vagotonia, sympathicotonia or hypo-adrenalinism. Indeed, a term might be coined to indicate a disturbance of liver function that could also give rise to the symptomatology.

The rôle of this syndrome in the production of idiopathic epilepsy has already been discussed (Nielsen and Eggleston: *J. A. M. A.* **94**:860, 1930), and several cases have been reported in which hypoglycemia seemed to be the cause of the seizures. Other important papers dealing with this syndrome have appeared (Howland et al.: *J. A. M. A.* **93**:674, 1929. Wieden et al.: Carcinoma of the Islands of the Pancreas, Mayo Clinic. Allen et al.: The Surgical Treatment of Hyperinsulinism, Mayo Clinic).

I have been following the question of blood sugar in epileptic patients for some time, and have noticed a tendency to hypoglycemia. But the work of Lennox (Arch. Neurol. & Psychiat. **18**:395, 1927) tended to show that hypoglycemia could not be causative, and that it was not even a constant observation.

However, when dextrose tolerance tests were carried out to the third, or much better to the fourth, hour in these patients, some surprising results were obtained. The technic of the test when it can be carried out as preferred is as follows: A

starvation blood sugar determination is made in the morning, after which a solution of dextrose containing 1.75 Gm. per kilogram of body weight is ingested by the patient. Blood sugar determinations are then made at one-half, one, two, three and four hours after ingestion. The results in a series of cases are shown in the table.

It will be seen by reference to the table that hypoglycemia is indeed not constant, but that it did occur in every case at some time during the course of the test. In certain cases the absence of any rise in the blood sugar after ingestion of dextrose is at least striking. The first three curves are from cases previously reported (Nielsen and Eggleston). At the time of that report it was stated that treatment with suprarenal substance had had no effect on patients with idiopathic epilepsy. It was believed that only a small group of cases of hyperinsulinism could be culled from the large group of those of idiopathic epilepsy. But dextrose tolerance tests were not conducted as a routine until recently, and the surprising results shown were obtained.

The table shows serial cases of idiopathic epilepsy. No selection has been made except to diagnose each case as the patient was seen and to advise appropriate

Dextrose Tolerance Curves *

	Starvation	½ Hour	1 Hour	2 Hours	3 Hours	4 Hours
1	94	110	93	101	54	84
2	93	143	114	93	64	73
3	83	128	149	34	63	69
4	97	...	160	142	69	..
5	80	109	67	75	73	65
6	86	86	82	80	80	..
7	72	80	105	100	80	..
8	71	83	54	54	60	..
9	80	81	97	62	75	..
10	83	90	105	60	71	..
11	83	83	86	74	57	..
12	115	128	65	128	112	110
13	102	129	162	106	65	75
14	85	122	100	97	72	89

* Cases 4 to 14 inclusive are serial cases, excluding only those in which a definite cause could be determined and those idiopathic cases in which a dextrose tolerance test was not obtained.

treatment when a cause of the seizures could be determined. All cases in which a cause for the attacks was found were excluded from the study.

The constancy with which hypoglycemia occurs in the course of a dextrose tolerance test in these patients cannot be merely a coincidence. The questions arise whether this is a daily occurrence and whether the hypoglycemia causes the convulsions. In the present state of our knowledge, it is unsafe to postulate either a daily occurrence or causation. It is known that dextrose is a strong stimulant of the internal secretion of the pancreas, and it is thought that a lower blood sugar level occurs in the course of a dextrose tolerance test than after an ordinary meal. However, patients may ingest an excess of sugar at any time and thus cause hypoglycemia. But why do not these patients have a seizure during a dextrose tolerance test? Vagotonic patients under examination by me have lost consciousness during a test, but never an epileptic patient. Perhaps my experience is not wide enough and my knowledge of body chemistry too meager. Dr. Lewis and I have found and reported previously (*Arch. Path.* **3**:212, 1927) that a hypoglycemic reaction is not necessarily simultaneous with the greatest hypoglycemia. Moreover, neither the reaction nor the hypoglycemia is confined, by any means, to epilepsy. There are undoubtedly other factors, still unknown, involved.

A system of therapy has been devised based on the influence of hypoglycemia as a causative factor. 1. The patients are fed six times a day, and in rare cases in which it is definitely indicated, eight times. This cannot but aid in the maintenance of a higher blood sugar level. 2. Sugar and sweets are excluded from the

diet because of their stimulating effect on the production of insulin. 3. When indicated and shown to be effective, suprarenal substance is given by mouth to aid in maintaining a higher level of blood sugar. Other forms of treatment are also used, as follows: 4. Fluid intake is restricted, because Fay (ARCH. NEUROL. & PSYCHIAT. **23**:920, 1930) has shown that dehydration is beneficial and because excess of liquid means excess of base (Peters: The Regulation of Acid-Base Equilibrium, Oxford Loose-Leaf Medicine, vol. 6, chapter 6). Alkalization aids in the production of epileptic seizures. 5. A moderate (and in severe cases, strict) ketogenic diet is enforced. 6. Calcium is given by mouth, because it tends to reduce seizures. 7. Cod liver oil is given to aid in the absorption of calcium. 8. Phenobarbital is given only if the other methods mentioned fail.

Without sufficient cases to draw conclusions, only a general impression is here expressed that with the method of treatment described, without phenobarbital, the results are several times as good as they were three years ago before this therapy was known.

HYPERINSULINISM, WITH REPORT OF A CASE. DR. EUGENE ZISKIND.

Hyperinsulinism is a relatively new clinical syndrome with symptoms similar to those attributable to overdosage with insulin. The cardinal features of the syndrome are: 1. A group of symptoms such as might occur from insulin shock in a diabetic person—tremor, tachycardia, weakness, paresthesias, perspiration, hunger and impairment of consciousness. There may also be dilatation of the pupils and any of a whole gamut of neurologic symptoms, including convulsions and palsies of the cranial nerves and extremities. 2. Relief from symptoms by ingestion of food or the intravenous administration of dextrose. 3. Hypoglycemia. 4. Decreased dextrose tolerance (as in diabetes). Because of this type of curve (usually thought of as indicative of hypo-insulinism) and marked variations in consecutive dextrose tolerance tests, the term dysinsulinism has been applied to this syndrome. 5. The absence of a rise in blood sugar following the injection of epinephrine or solution of pituitary. Symptoms 4 and 5 are inconstant.

Although this syndrome has been recorded in connection with lesions of the liver and suprarenals, the greater number of cases have shown a pathologic condition in the pancreas. Many of these patients go to neurologists for diagnosis.

REPORT OF CASE.—A youth, aged 19, was a senior high school student, employed intermittently at night as a bell boy in a hotel. On the evening of Sept. 5, 1930, he complained of headache and dizziness. In the morning he stood up from the breakfast table, stared at his mother and fell to the floor with twitchings of the right arm and leg. He was "dazed" for a few minutes. Later, more twitchings developed, and he remained in the "dazed" condition until 5 p. m. He then suddenly became normal. The next morning he again had a convulsion, and this time did not regain consciousness for several days. He was admitted to the Los Angeles County General Hospital on September 8, in coma.

The history of the patient revealed that during the year and a half previous to admission he had had spells of trembling, weakness and mental clouding occurring at about noon, which he himself attributed to waiting until 1 p. m. for lunch. He had had occasional headaches for eighteen months, which were relieved by lying down and by evacuation of the bowel. The family history yielded the information that the patient's maternal grandfather had had diabetes. The mother's sister, great aunt and two cousins had goiters. The father and his brothers were all tall and stout.

The results of physical examination were as follows: The patient was in coma; the temperature was 102 F., and the pulse rate 90. A cleft palate and hare lip had previously been repaired. The heart and lungs were normal. The blood pressure was 120 systolic and 85 diastolic. The abdomen showed no masses, tenderness or rigidity. There was hemiparesis of the right side with a positive Babinski sign on that side, a double Babinski sign on the left side and nystagmus. There were slight rigidity of the neck and slight congestion of the optic disks.

The laboratory tests showed that, on September 8, the blood sugar was 40 mg. per hundred cubic centimeters; no urine was obtained on catheterization. On September 9, however, the urine showed: albumin, 3 plus; many pus cells; an occasional granular cast, and specific gravity, 1.037. The white blood count was 11,800, with 67 per cent polymorphonuclears. The spinal fluid was clear, under normal pressure, containing 3 cells per cubic millimeter, a normal amount of sugar and a trace of globulin. On September 10, chemical examination of the blood showed: nonprotenin nitrogen, 35, and blood sugar, 58. Roentgen examination of the skull revealed nothing abnormal. On September 11, the dextrose tolerance test showed: after fasting, 56 mg.; in one-half hour after the ingestion of food, 109 mg; in one hour, 160 mg; in two hours, 222 mg, and in three hours, 186 mg. The reaction to epinephrine (10 minims, 0.6 cc.) was as follows: blood sugar before administration, 186 and fifteen minutes after, 186 mg. The reaction to solution of pituitary (1 cc.) was: blood sugar before injection, 146 mg., and fifteen minutes after, 146 mg.

On September 12, the patient shook his head in the affirmative and negative in response to questions, though he did not speak and for the greater part of the time was in stupor. Careful daily examinations of the nervous system revealed fluctuation of neurologic symptoms. The hemiparesis was at times questionable. At other times there was bilateral extensor rigidity of both arms and legs, with bilateral clonus, and sometimes a bilateral Babinski sign. On September 16, although the patient was receiving dextrose daily, an effort was made to determine the amount necessary to keep the blood sugar above normal limits during the entire twenty-four hours. It was found that 200 Gm. of carbohydrate daily would probably keep the patient free from hypoglycemia. Hence rigid control was maintained for forty-eight hours by the administration of 60 Gm. of dextrose intravenously every eight hours. On the following two days, definite improvement from coma was apparent. The patient was conscious on September 22, and though he did not speak, showed apraxia. On September 27, anomia was noted.

On October 1, Dr. I. L. Meyers detected a right homonymous hemianopia. Because of the anomia and the hemianopia, it was thought that the neurologic lesion was in the region of the angular gyrus of the temporal lobe, extending posteriorly or internally so as to involve the optic radiations.

The patient was up and about the ward, clamoring to go home and eating on all occasions. He ate two or three trays of food at every meal, and frequently ate between meals, also at 2 a. m. Once, when the 2 a. m. feeding was omitted, he walked down the fire escape, apparently asleep. At another time he walked to the center of the ward and urinated on the floor. The next morning he denied all knowledge of these episodes.

On October 6, food was withheld to see whether the patient still had the tendency to hypoglycemia, and blood sugar readings were taken every hour. The blood sugar level dropped consistently, and symptoms of insulin shock supervened. With a blood sugar of 52 mg. the patient was quite drowsy.

The impression was that the syndrome of hyperinsulinism was probably due to a lesion of the pancreatic islets, with secondary cerebral thrombosis.

Comment.—This case is presented to demonstrate the syndrome of hyperinsulinism. The anatomic substratum for this clinical picture has not been definitely decided. The present case differs in one important respect from others cited in the literature: The patient presented certain neurologic phenomena which persisted even after the blood sugar was elevated to normal. The hemiparesis, the coma and then the aphasia were present for a short time after the blood sugar was kept at a normal level. The hemianopia has persisted to the time of presentation. The neurologic conditions have behaved much as in cerebral thrombosis and have largely disappeared. At present, the patient still shows the phenomena of hyperinsulinism whenever food is withheld. Whether the hyperinsulinism is due to an intra-abdominal lesion or to one in the brain is still a question.

A primary or sole neurologic lesion appears unlikely for the following reasons:

First, the course of the neurologic phenomena is that of a vascular lesion, probably cerebral thrombosis. But the latter would not have produced attacks of weakness and mental clouding over eighteen months and then have culminated in coma. A brain tumor with a sudden hemorrhage into it might give this picture, but one would expect more signs of increased intracranial pressure and more residual localizing signs.

Second, a brain lesion giving this picture would in all probability be located about the hypothalamus, the center for many visceral functions. Our neurologic observations do not indicate this location.

Third, neurogenic disturbances of sugar metabolism are usually not amenable to dietary control and are transient. This patient's hypoglycemia is controlled well by diet and, at least to the time of this meeting, shows a permanent tendency. Whether the lesion causing the hypoglycemia is in the pancreas, liver or suprarenal cortex has not as yet been ascertained, but since in most cases the condition occurs in the pancreas the pathologic process is tentatively considered as being located there.

DISCUSSION

DR. CYRIL COURVILLE: The question of the relationship of certain metabolic disorders to local lesions of the thalamencephalic floor is being emphasized more and more. Recent anatomic, pathologic and experimental studies point to this region as a possible source of such manifestations. Morgan and Johnson observed convulsive seizures following experimental lesions of the tuber cinereum in animals. This led to a study of the region in the brains of epileptic persons. Regressive changes were found in the nerve cells constituting the nuclear masses of the thalamencephalic floor and wall. Whether these changes were purely local or a part of a general pathologic picture in all parts of the brain was not made clear.

Clinical studies, furthermore, appear to support the conception of a center for control of carbohydrate metabolism in the neurohypophysis. This is considered to include the posterior lobe of the hypophysis and the regional thalamencephalic floor with which it is connected by nervous pathways in the infundibulum. Dr. Nielsen now finds a tendency to hypoglycemia in a group of epileptic patients in whom no other attributable cause was discovered to explain their seizures. Complete or partial relief from convulsions by increasing the amount of carbohydrate ingested suggests that this low blood sugar may have a causative relationship. The question now arises, can this disturbed carbohydrate metabolism be attributed to regressive changes in the nerve cells of the tuber cinereum or in the connections with the hypophysis?

Whether or not the question will be answered in the affirmative, further studies of the function of this so-called primitive portion of the brain will undoubtedly bring to light much of importance in respect to the metabolic activities of the body.

NEW YORK NEUROLOGICAL SOCIETY AND NEW YORK ACADEMY OF MEDICINE, SECTION OF NEUROLOGY AND PSYCHIATRY

Joint Meeting, March 10, 1931

S. PHILIP GOODHART, M.D., *President, in the Chair*

MULTIPLE SUBCORTICAL VENOUS ANGIOMAS. DR. CHARLES DAVISON.

W. W., a man, aged 59, was admitted to the Montefiore Hospital in February, 1930, with the complaint of dyspnea on slight exertion and paralysis of the right half of the body. In February, 1929, he had noticed edema of the lower extremities,

and the following August, while he was sitting in a chair, paralysis of the right half of the body had suddenly developed.

General examination showed: a slightly enlarged heart, with accentuation of the second aortic sound and a short and soft systolic aortic murmur; a tender and enlarged liver, 10 cm. below the costal margin; edema of the lower extremities, and a blood pressure of 185 systolic and 105 diastolic.

Neurologic examination revealed: inequality of the pupils, the right larger than the left, which reacted somewhat sluggishly to light; pinpoint hemorrhages in the retina, and sclerosis of the retinal veins; deviation of the tongue to the right; flaccid paralysis of the right upper and lower extremities, with a slight hyperreflexia and a Babinski sign on the right, and a slight impairment in vibration sense in the right lower extremity from the toes to the iliac crest. The sensory status was otherwise normal.

During the patient's stay in the hospital, he became markedly dyspneic and cyanotic; Cheyne-Stoke's respiration developed, and he became stuporous and died of terminal bronchopneumonia three weeks after admission.

A roentgenogram showed a moderate enlargement of the left ventricle and dilatation of the entire thoracic aorta. An electrocardiogram showed a bundle branch block, approaching an arborization block. All other laboratory data were negative.

The clinical diagnosis was: cerebral thrombosis, right hemiplegia, generalized arteriosclerosis, hypertensive heart disease and terminal bronchopneumonia. The anatomic diagnosis was: arteriosclerosis of the coronary and cerebral vessels, cardiac hypertrophy and dilatation, hemorrhagic bronchopneumonia and healed infarct of the left ventricle.

Gross examination of the brain showed atherosclerotic changes in the vessels at the base. On horizontal section, numerous small masses, varying in size, blood-tinged and firm, were scattered over the right centrum ovale (slightly above the corpus callosum), the septum pellucidum, the left putamen, the left occipital lobe and the pons.

Sections of the subcortical masses were stained by the Weil, hematoxylin and eosin, van Gieson, cresyl violet and Perdrau methods, and examined microscopically. The tumor-like masses consisted of a number of vascular channels of varying caliber and with thin walls; some looked cavernous. The intima consisted of a single layer of endothelial cells. None of the vessels showed evidences of an elastica interna. The media, which was small, consisted of a few smooth muscle cells scattered in the hyalinized connective tissue. The adventitia consisted of a few strands of fibrous connective tissue. Evidences of leiomyomas were found in the walls of some of the vessels, which were thickened, owing to hyaline transformation. In places, between the vascular channels, normal and proliferated glia replaced the nerve cells. Occasional intimal proliferation of the smaller capillaries was found, and there was capillary proliferation in the region of the septum pellucidum, near the large vascular channels.

A diagnosis of multiple subcortical venous angiomas was made.

INTRAMEDULLARY NEOPLASM OF THE CORD WITH HEMATOSYRINGOMYELIA. DR. CHARLES DAVISON.

W. R., a boy, aged 14, was admitted to the Montefiore Hospital in April, 1930. In 1927, the parents noticed that the child limped and that the left lower limb was becoming shorter. Three years later, this was followed by scoliosis; a diagnosis of poliomyelitis was considered. In January, 1930, three months before admission and three years after the onset of the limping, as the patient was walking up the stairs in school he experienced pain in the back with weakness of both lower extremities, and he fell on his elbow. He managed to walk home that day without assistance. Two days later, he became incontinent and was unable to move the left leg or to stretch the fingers of the left hand. He was taken to Mount Sinai Hospital where a diagnosis of syringomyelia, with a complete block at the fourth cervical segment, was made. A laminectomy, per-

formed in May, 1930, by Dr. Ira Cohen, disclosed a hematomyelia at the fifth cervical segment. Following the operation, signs of a complete transverse lesion of the cord developed.

General examination revealed a pigeon-breast deformity, a rapid heart rate (100) and a distended bladder leading halfway to the umbilicus.

Neurologic examination showed: diminution of motor power in the upper extremities, which was more marked on the left; flexion of the fingers of the left hand, especially those of the ulnar side; paraplegia, and generalized muscular wasting. All of the tendon reflexes were absent, except the biceps. The Babinski reflex was not elicited. There was incontinence of urine and feces. Sensation produced by touch, pain and temperature was diminished from the eighth cervical segment down on the left side and from the second dorsal segment on the right side, and there was a loss of vibration from the toes to the hips as well as a loss of the sense of position in the toes.

A roentgenogram disclosed a lower dorsal scoliosis. A Quenckenstedt test showed a complete block. There was a Froin syndrome. Following this procedure all the sensory signs disappeared. Injection of iodized poppy seed oil 40 per cent by the cisternal route showed a complete arrest of the oil at the fourth cervical vertebra; following this, the sensory impairment returned with a zone of hyperalgesia between the third and the fifth cervical segments. All other laboratory data were negative.

In August, 1930, atrophy without fibrillations was noticed over the left thenar, hypothenar and interosseal muscles. The sensory level descended to the seventh dorsal segment. In November, 1930, convulsions developed and the patient became drowsy and comatose. Examination revealed a bilateral papilledema, a rigid neck, exaggerated knee jerks, a pulse rate of 120, a temperature of 99.9 F. and a blood pressure of 200 systolic and 160 diastolic. The urea nitrogen was 59, and the creatinine, 1.2 mg. The patient died on November 3.

The anatomic diagnosis was: intramedullary neoplasm of the spinal cord, scoliosis of the vertebral column, hypertrophied bladder, bilateral hydronephrosis and localized pericarditis.

Gross examination of the spinal cord showed that it was markedly swollen, especially in the upper dorsal region. There was engorgement of the vessels of the cord. Section of the cord revealed a cavity surrounded by whitish, firm tissue between the second and the fourth cervical segments. From the fifth cervical to the first dorsal segments the cavity was markedly enlarged; it contained blood and displaced most of the substance of the cord. Between the second and the fourth dorsal segments the bulk of the substance of the cord was filled with gelatinous tumor tissue and organized clot. The outer walls of the cord were whitish and felt firm. Part of the tissue of the tumor was found as far down as the first lumbar segment. All of the lumbar segments contained a slitlike cavity which ran in the anteroposterior direction of the cord. This cavity assumed larger proportions in the sacral segments, where it replaced the greater part of the substance of the cord.

Frozen paraffin and celloidin sections of the tumor and spinal cord were stained by the Bielschowsky, Rio-Hortega, Cajal gold sublimate (Globus' modification), Victoria blue, Perdrau, hematoxylin and eosin, Mallory phosphotungstic and cresyl violet methods, and examined microscopically. In places, the tumor consisted of densely packed cells. Most of the cells were irregular, with little cytoplasm and few processes, and contained round and oval vesicular nuclei. Others, less numerous, were irregular and had deeply staining nuclei. Numerous giant cells and spongioblasts and occasional ependymal cells were also seen. Most of the cells were those seen in the medulloblastomas and protoplasmic astrocytomas. Evidences of hemorrhage, hyalinization of the vessels and organization were also observed. The tissue adjacent to the tumor consisted of glia tissue in which were found numerous giant astrocytes of the protoplasmic and fibrillary types. Inflammatory cells — a reactive phenomenon — were found in the meninges and spinal cord, mostly in the vicinity of the anterior spinal vessels.

The cavitations for the most part were lined by endothelial cells. In most of the segments, the walls of the cavity consisted of rows of glia nuclei with few fibers, a layer of proliferated blood vessels and an outer layer of glia fibers. In some places, hemorrhages were also found within their walls. At the tenth dorsal segment the slitlike cavity had the same histologic appearance, except that in one area the inner wall was lined by ependymal cells. This was the only evidence of a relationship between the cavity of the tumor and the central canal. The cord in the region of the tumor and the larger cavities were destroyed. The myelin sheaths were disintegrated, and the axis cylinders were broken down. Whatever anterior horn cells were left were found to be fairly intact. Of all the structures of the spinal cord, the anterior horn cells were the best preserved.

The microscopic diagnosis was: intramedullary neoplasm of the cord (astrocytoma), hematomyelia and syringomyelia — the end-result of a neoplasm.

It is difficult to label this tumor, and the term chosen was used because of the predominance of the cells described. Evidences of other elements, such as ependymal cells, spongioblasts and giant cells, were also found. It must be emphasized that, in labeling the gliomas, one should not adhere to a strict classifition, but should name these tumors in accordance with the type of cell that predominates.

TUMORS OF THE CEREBELLUM. DR. LEWIS STEVENSON.

The two tumors demonstrated appeared to be derived from the granular layers of the cerebellum and were, therefore, neuroblastomas or, more specifically and usefully, perhaps they might be called granuloblastomas.

Dr. Stevenson had previously classified these two tumors as medulloblastomas, since they fit the description of such tumors very well, although one of them was not in the midline but was a large tumor of one of the cerebellar hemispheres.

Whether or not other medulloblastomas might sometimes develop in the same manner as the two tumors presented is a question of some interest. After all, the medulloblast is a hypothetic cell. Indeed, in one of his papers on gliomas, Bailey said: "especially hypothetic are the medulloblasts," and later, "the component cells of the medulloblastoma for the most part do not have morphologic characteristics that can be sharply displayed by special staining methods."

From the medulloblast Bailey derived not only the tumors he called medulloblastomas, but also, as shown in his diagram, the oligodendroglia. In 1930, Rio-Hortega, in a paper on the oligodendroglia, said that these cells are not derived from medulloblasts or indifferent cells, but directly from the gliocytoblasts, as he showed in his diagram.

The whole question so far has rested on Schaper's hypothesis, as shown by His, that all of the germinal cells in the medullary epithelium do not form nerve cells, but that some of them remain indifferent cells and are bipotential; that is, they have the power later to form either neuroblasts or spongioblasts or, indeed, to remain indifferent.

These hypothetic, indifferent cells (medulloblasts) have been supposed to give rise to tumors and malformations of the brain. It is worthy of note that Schaper was interested in the so-called indifferent cells of the outer granular layer of the cerebellum, from which it is believed the two tumors presented are derived. He held the opinion that these granule cells of Obersteiner's layer gave rise to both nerve cells and neuroglia cells in the cerebellum. Cajal and others did not agree with him in this and felt convinced that the neuroglia cells of the cerebellum were all derived from the epithelial cells, and that the germinal cells gave rise only to neurons. The indifferent cells, in the way Cajal used the word, were merely neuroblasts that would later produce neurons, and were by no means bipotential cells.

Photomicrographs and two drawings from Cajal showed that the granule cells of the cerebellum are actively dividing, migrating and changing from simple undifferentiated cells into complicated neurons, not only during the intra-uterine

life of the human embryo, but also for some time after birth. Such cells, at first undifferentiated and rapidly dividing and changing, might easily be supposed to give rise to tumors.

The first patient (Mrs. A. B.), a woman, aged 29, had complained of occipital headaches for two months and of blurring of vision for one month prior to admission to the Bellevue Hospital (service of Dr. Foster Kennedy). She had also had attacks of vomiting and dizziness and a tendency to fall backward. Her speech later became disturbed, and she had ataxia of the arms. She had choked disks and a fine horizontal nystagmus; there was no Babinski sign. The illness lasted for about two and one-half or three months. She was operated on and died.

The second patient (C. B.), a colored boy, aged 16, gave a history of trauma four months before the onset of the symptoms. For four weeks he had complained of occipital headaches on getting up in the morning, which became worse when he walked or worked. He occasionally vomited; there were choked disks and some stiffness of the neck — he held his head backward and to the left. There was no Babinski sign. He had slight ataxia of the arms and legs. He was ill for about two months and died suddenly after a general convulsion. An autopsy showed marked internal hydrocephalus, with a large, mottled, grayish tumor in the right side of the cerebellum.

ANATOMICOPATHOLOGIC CONSIDERATIONS OF THE PERIPHERAL NERVES. DR. GEORGE B. HASSIN (by invitation).

This article will be published in full in a later issue of the ARCHIVES.

THE CLASSIFICATION OF GLIOMAS AND THE TYPES OF NEUROGLIA CELLS. DR. WILDER G. PENFIELD.

This article will be published in full in a later issue of the ARCHIVES.

DISCUSSION

DR. SAMUEL T. ORTON: I am not in a position to discuss the paper of either Dr. Hassin or Dr. Penfield at great length. Dr. Hassin has reviewed in delightful form the relative importance of the mesodermal and ectodermal tissues in their interplay within the nerve bundles.

I admire not only the material that Dr. Penfield has presented, but the attitude of mind that brings him before us, ready to challenge certain didactic or dogmatic concepts in the field of tumors of the brain. I was particularly interested in his reference to the importance of considering pathologic pictures of the neuroglia cells in the interpretation of tumor patterns. Obviously, the growth and architectural features under which tumor cells develop are different from those under which a normal cell exists. Not only are there differences of a chemical nature, but the architectural features are also different. I think that the picture he has presented as "hairy" neuroglia is similar to that which one sees in columnar replacement by glia cells in cases of tabes. Here the form is modified by the fact that it is longitudinally replacing progressively degenerating nerve fibers. One after another of the posterior fibers drop out, and the form of the neuroglia cells is determined by the fact that it is a replacement of the former columnar structure. When the replacement takes place in the less orderly structures of the cerebrum, one finds a different picture. Here the result is a tangled scar. Similarly, it is obvious that one would not find the same type of cells in the rapidly growing tumors as in the more highly differentiated and slower growing ones that are more closely related to the formation of a glia scar.

Another point made by Dr. Penfield that must be taken into consideration in all tumors is the wide range of differentiation of cells in practically any tumor of a single group. I think that adequate search in almost any tumor will reveal cells that represent two or more stages in the development of that type. From the histologic standpoint, the practical issue seems to me to be the question of

what criterion shall be used in classifying these tumors. General pathologists are prone to name a tumor from the least developed element that it contains, and not from cells that are best represented numerically. The tendency is derived from the belief that the cell with the least differentiation is the one that in the long run will determine the malignant condition. Whether that is an acceptable basis for classification remains open to discussion. Meanwhile, it will make a marked difference in our envisagement of the comparative incidence of a type of tumor if one assigns it a name on the basis of the preponderance of a given type or on the basis of the lowest type present.

DR. CHARLES A. ELSBERG: If I venture to say a few words on Dr. Penfield's paper, it is because, as a neurologic surgeon who deals with the problems of the treatment for gliomas, I am greatly interested in the correlation of the pathologic histology of these tumors with their clinical course and with the results that can be obtained by surgical intervention.

The classification of gliomas proposed by Bailey and Cushing was a great advance. No one can realize this better than he who has lived through the days when all such tumors were called gliomas and no distinctions were made between different types, no matter what their course or their pathologic characteristics. One spoke of them merely as soft or as solid gliomas, and there was no correlation of the different types with the varying clinical course. It was extremely helpful when these tumors were distinguished from each other on the basis of their more or less differentiated glia cells. This advance was greatly aided by the work of Globus and Strauss on the tumor they called spongioblastoma multiforme, and also by the studies on glia and on glial tumors by Dr. Penfield.

During the past few years, I have been greatly interested and also puzzled about some tumors of the glioma group. I shall put my thoughts in the form of questions to Dr. Penfield. 1. Does the so-called medulloblastoma, whether or not it is a true gliomatous tumor, belong where it has usually been placed in the scale, as the most unripe and undifferentiated form of glial growth? From the characteristics seen at the time of operation and from its clinical course both before and after radical or conservative surgical procedure, I have gained the impression that the medulloblastoma belongs lower in the scale than the spongioblastoma multiforme. Of course, the medulloblast is a theoretical conception, and if the medulloblastoma is really a glial tumor, I suspect that it belongs somewhere between the astroblastoma and the astrocytoma. 2. How should one classify the different glial tumors, placing for the moment the astrocytomas at one end of the scale and the spongioblastoma multiforme at the other? It is not rare to find changes in the blood vessels and areas containing spongioblasts in the histology of the astrocytoma; vice versa, in the spongioblastoma multiforme, one can always find areas made up of astrocytes. The clinical course of an astrocytoma may be slowly progressive, which is characteristic of this type of growth. At operation, the appearance is that usually seen in astrocytomas. If there is a recurrence after six or eight months or after several years, the symptoms may be acute and may advance rapidly. At the second operation, the gross appearance of the recurrent growth has changed. It now looks like a typical spongioblastoma, and the pathologic report is "spongioblastoma multiforme."

If the pathologist finds an area of carcinoma cells in a supposed adenoma of the breast, he will call the tumor an adenocarcinoma. If such a growth had been incompletely extirpated, a recurrence would have the histologic and clinical characteristics of a carcinoma and not of an adenoma. Is it not the case, as mentioned by Dr. Orton, that the reason why an astrocytoma may recur as a spongioblastoma multiforme is because the most undifferentiated cells, i. e., the spongioblasts, grow most rapidly and they, rather than the astrocytes, form the bulk of the recurrent growth? If this point of view is correct, it is the cell type itself rather than the predominance of one or the other type that is of importance. Is it therefore entirely correct to speak in most instances of astrocytomas or of spongioblastomas? Many of the astrocytomas contain highly malignant cells, and would it not, therefore, be more in line with the facts to call

such growths spongioblastic astrocytomas, and in a similar way to refer to some spongioblastomas as astrocytic spongioblastomas? In this way, special stress would be laid on the presence in the one case of areas of more rapidly, and in the other case of more slowly, growing cells.

With reference to what Dr. Penfield has said on the subject of calcification as an evidence of the slowly growing character of a glioma, I would mention that in our clinic Dr. Masson has investigated the subject and has found that calcification is as visible on roentgenograms in cases of spongioblastoma multiforme as in those of astrocytoma.

DR. ARMANDO FERRARO: I heartily agree with the remarks concerning the connection of the peripheral nerves with the subarachnoid and subdural spaces. It is of great importance to bear in mind such connections, and Dr. Hassin has given an excellent and convincing illustration of these connections. The knowledge of such a fact facilitates the comprehension of the possibilities of diffusion of infectious conditions from the periphery to the central nervous system.

I have also been greatly interested in Dr. Hassin's discussion of the participation of the mesodermal component in the processes of degeneration and regeneration of nerve fibers, and have been especially impressed by the fact that the cells of Schwann disappear by transformation into gitter cells and therefore are no longer present in the peripheral portion of an injured or sectioned nerve. The theory, therefore, that attributes a chemotactic power of attraction to the cells of Schwann in the process of regeneration cannot hold true, and one must look to the proliferated endoneurium for such a display of chemical attraction.

I am less impressed, however, by the supposedly important function of the mesodermic tissue in the formation of gitter cells. I may appear skeptical, but it seems to me that the whole conception of the transformation of cellular elements into gitter cells may undergo a change. There are too many elements that are transformed into gitter cells: the microglial elements; for some authors, the oligodendroglia; various hematogenous elements; some endothelial cells, and now the cells of Schwann. Too many disparate elements are said to undergo such a transformation. This fact naturally brings to mind the question whether, in the formation of gitter cells, one is really dealing with an active process of transformation intended to elaborate products of disintegration, or whether one is not more probably dealing with a process of degeneration without any specific activity involving so many elements. The question is a complicated one to discuss at length, but I wanted to formulate it as it came to my mind a long time ago.

The work of Dr. Penfield on the clinical classification of these tumors is of great value, and I subscribe to his attempt to limit the classification as much as possible, and to try and correlate the pathologic aspects of the tumors with their clinical course. While I agree with this attempt, which will turn out to be useful from a practical standpoint, from a more scientific and technical point of view, I should like to have the door open for a more detailed investigation of each tumor and a detailed description of its histologic features; I should even go so far as to recommend, when possible, the study of serial sections of tumors in order to detect all the various types of cells that form the mass of the tumor. It will be through accurate reports of the variations in the structure and emphasis on the various areas formed by elements different from those that constitute the bulk of the tumor that one may be able to enlighten situations, such as Dr. Elsberg pointed out concerning the transformation of a benign tumor into a more malignant type. It will be through the detailed study of serial sections of a tumor that questions may be answered pertaining to the development of the various elements, which pure embryologic study may fail to elucidate. Such an opportunity, for instance, has arisen in one of my cases of a mixed type of glioma in which I was able to study, in some of the areas presenting the structure of an oligodendroglioma, the derivation of these particular cells from the polar spongioblasts.

Concerning the process of calcification, I wish to ask Dr. Penfield if he has made any particular study of the calcified areas that are found not only in oligodendrogliomas but also in other tumors, such as the astrocytoma and spongio-

blastoma multiforme, as pointed out by Dr. Elsberg. Is it possible that one common type of cell present in all these various tumors might degenerate and therefore appear calcified, or is the process of calcification independent of any particular cellular involvement and analogous to that occurring in a general pathologic process?

DR. LEON H. CORNWALL: It has been a great satisfaction to hear Dr. Hassin review the subject of the histology of the peripheral nerves, and to emphasize a point that is not yet recognized by the authors of some textbooks; namely, that certain of the sheaths that have been described—the Schwann, the myelin and the axolemma—do not exist as separate structures. The Schwann cells are syncytial, and myelin is a component of their cytoplasm. Although I do not disagree with anything that Dr. Hassin has said, I am not able from my own experience to say definitely that the Schwann cells disappear entirely from the distal segment of a cut nerve and that all of the nuclei that are seen are of mesodermal origin. This view is unorthodox, but, realizing that Dr. Hassin's conclusions are based on careful observations, it has weight.

The communication between the epineural, perineural and endoneural spaces and the subarachnoid space is again a logical conception. Only a few years ago, Goodpasture showed that certain particulate materials pass by way of the axons from the peripheral to the central nervous system. My recollection is that he injected certain toxic agents into the masseter muscle and later found inflammatory changes in the nucleus masticatorius on the side of the injection. There was no inflammatory reaction, however, in the meninges at the emergence of the fifth nerve.

Only a few years ago, under the title "Meningo-Encephalic Carcinomatosis," I reported a diffuse distribution of carcinoma cells in the subarachoid space and its perivascular prolongations, without nodular tumor masses in the brain or the meninges. The diagnosis rested entirely on the microscopic picture. The primary growth in that case, a colloid carcinoma, was in the mucous membrane of the stomach. Similar collections of tumor cells were noted in the vicinity of the nerves in the wall of the stomach, as well as in the sheaths of the nerves in the skin of the thorax and the abdomen.

Any simplication of the unwieldly nomenclature for glial tumors is to be welcomed with enthusiasm, and I heartily approve of what Dr. Penfield said. I wish to ask a question as to his meaning in using the term "migratory" for the apolar spongioblasts. If he used migratory in the sense that the spongioblasts have not yet become attached to blood vessels or to a mesodermal membrane, he is correct; however, most spongioblasts are migratory, except those that remain near the lining of the neural tube and presumably become ependyma cells.

The tumors presented by Dr. Stevenson were unusual, and I am certain that further work will develop debatable points in their classification. I wish to ask Dr. Stevenson if he considered that these tumors might be neurospongioblastomas, a term that Dr. Globus has recently used.

DR. JOSEPH H. GLOBUS: To say anything about Dr. Hassin's presentation would mean praise, and to praise would detract from its excellence by unnecessary repetition.

Dr. Penfield raised the question of the dominance of a cell type in tumors and its bearing on the naming of tumors. One must still be guided by the dominance of cell type when labeling, grouping and classifying tumors. One can often recognize the existence within a certain tumor of islands of some other neoplastic elements that do not exactly correspond to the dominant cell type. For example, a tumor that throughout numerous microscopic fields appears to be gliomatous or astrocytomatous may present within a single field collections of cells that suggest the structure of spongioblasts. Shall the tumor therefore be called a spongioblastoma because it has a few islands of spongioblasts, or shall it be named a glioma or an astrocytoma because the dominant cell type is glial? I think that one might reasonably call such a tumor an astrocytoma, with the reservation

that the tumor has spongioblastic islands. This would be done in order to describe the tumor more accurately, and so give warning that it has the potentiality of a malignant growth.

The second point raised by Dr. Penfield is whether spongioblastomas are tumors in the full sense of the word. Are they no more than an expression of a reactive phenomenon because, in his opinion, they are so different from other gliogenous tumors and do not fit into the general group of gliogenous growths? Are, then, the spongioblastomas tumors or are they glial phenomena reactive to some other lesion of the brain, not of neoplastic origin? I think that the answer to this question has already been hinted by Dr. Elsberg, when he spoke of his experiences with tumors that were recognized definitely as gliomas of a benign form and which, in the course of events, changed into spongioblastomas. I have been able to report four cases in an article that will soon appear in the *Zeitschrift für die gesamte Neurologie und Psychiatrie*, in which I was able to follow the evolution of a spongioblastoma from a benign gliogenous tumor. Tumors that could not be called spongioblastomatous at first, later recurred and necessitated removal; one of them recurred three times, and finally assumed the character of a true and exceedingly malignant spongioblastoma. At each operation the tumor had become more malignant, until it was almost an explosive type of spongioblastoma. I think that this experience shows that spongioblastomas are unquestionably tumors, and that they represent a type separate and distinct from others.

There are several elements which form a link between the less malignant—the more differentiated—and the more malignant—the less differentiated—types of glioma. Spongioblasts represent a stage in the transition of the less differentiated cell type into a more differentiated form. The coexistence of a spongioblastoma with another form of blastomatous change in the brain is another feature in favor of its neoplastic character. In a large group of tumors I was able to establish the coexistence of lesions characteristic of tuberous sclerosis in this form of tumor. This association of spongioblastic types of tumors with another lesion of the character of diffuse neurospongioblastosis serves to support the contention that the spongioblastoma is a tumor. In every tumor, of course, a germinal center must exist. If there were no germinal centers in tumors, either benign or malignant, there could be no progressive growth. In order that tumors may grow, they must contain a primitive cell. Even in the more benign tumors, a number of primitive cells must exist. A tumor in which every cell has reached its full stage of differentiation cannot grow. The existence of germinal centers makes it impossible to make a clear distinction between a benign and malignant tumor. The transition from benign to malignant will always occur, and this will defeat attempts to classify tumors with a sharp line of distinction between malignant and benign. As far as tumors of the brain are concerned, they may be provisionally diagnosed as benign, but the existence of the germinal centers within that tumor must always be borne in mind, for they are the carriers of tendencies for a malignant process.

DR. GEORGE B. HASSIN: It is not possible in a little more than half an hour to cover the many problems relative to the anatomy, physiology and pathology of the peripheral nervous system, so in reply to Dr. Ferraro I must say that I did not have a chance to consider in detail all of the phenomena occurring in the mesodermal tissue.

DR. W. G. PENFIELD: I think that the question raised by Dr. Orton as to which cell is to be selected as the type cell of any tumor is a difficult one to answer. It is hard to select the most embryonic cell. One may see a cell that looks like a spongioblast, but unless the stains have been made carefully, one cannot be sure that it is a spongioblast. On the other hand, one can be sure of the type of cell predominant in a tumor. Perhaps the safest way is to make a classification according to the predominant cell type, for this gives the outstanding characteristic.

I was much interested in Dr. Elsberg's remarks about the early days of gliomas. It is interesting, too, that Tooth, when he made the first study of a large group

of gliomas, pointed out that there is a difference in them that is indicated to a certain extent histologically. He pointed out that in gliomas the formation of rings meant rapid growth, probably thus indicating the medulloblastomas. He also found that the appearance of giant cells means a malignant process; by this he doubtless referred to the spongioblastoma multiforme.

I did not understand the discussion of medulloblastoma. Did Dr. Elsberg mean that it was less malignant than had previously been assumed? He said lower in the scale.

DR. C. A. ELSBERG: I meant that the medulloblastoma was less malignant than the spongioblastoma multiforme.

DR. W. G. PENFIELD: Spongioblastoma multiforme, the most malignant of all gliomas, must be considered on one side. If one takes that out of consideration, the medulloblastoma will have to be considered high in the scale as far as recurrence is concerned and very low in the scale as far as cellular differentiation is concerned.

I have never seen an astrocytoma with perfectly definite spongioblasts in it. On the other hand, Cushing, and also Globus, described in one patient an apparent transition from an astrocytoma to a spongioblastoma multiforme. I presume that we must accept that as possible. However, if one takes a small piece of tissue and expects to make a careful classification on the basis of it, one is going to make mistakes. One may take out a piece of tumor and think that it is an astrocytoma when it is really a spongioblastoma multiforme. The histology of the blood vessels is the best differential guide in such a case.

Dr. Ferraro's observations about the developmental studies of tumors interested me, but it seems to me that tumors are not the place to study the development of neuroglia; one would achieve better results and make fewer mistakes if that were studied in the developing nervous system.

I have not made observations about calcification in these tumors, except that it has been shown that wherever degeneration occurs in the body calcification also occurs. Such calcification is often focal as well as perivascular.

I think that Dr. Cornwall's criticism of the term migratory spongioblasts is a good one. "Apolar" is a better name. They are all migratory.

Dr. Globus pointed out that spongioblastoma multiforme is a tumor and not merely a malformation. Certainly it is a tumor; it is neoplastic, but it is a tumor that illustrates a theory that has been proposed long before now, that the underlying change in a neoplastic growth may be a change in the blood vessels.

CHICAGO NEUROLOGICAL SOCIETY

Regular Meeting, March 19, 1931

SIDNEY D. WILGUS, M.D., *President, in the Chair*

LEFT HEMIHYPERTROPHY: REEXAMINATION AFTER TWENTY YEARS. DR. PETER BASSOE.

In April, 1911, I examined this patient, who was then 16 years of age, and later published an illustrated report (*Am. J. Insanity* **69**:91 [July] 1912). At birth, everything on the left side had appeared larger, and as the boy grew the same proportion was maintained, except that the right foot was also enlarged. The height then was 152 cm. The circumference of the right side of the chest was 34.5 cm., and of the left side, 37.5 cm. The length of the right hand was 16.5 cm.; that of the left, 18.5 cm. The distance from the anterior superior spine of the ilium to the inner malleolus was 74 cm. on the right and 78.5 cm. on the left. The right foot was 24.7 cm. in length; the left, 26.3 cm. Further measurements are given in

the aforementioned article. The many abnormalities of the skin, especially the vascular nevi, were described by Dr. Oliver S. Ormsby. Roentgenologic examination of the skull and extremities revealed nothing abnormal. In August, 1913, the height was 166.5 cm. The horizontal measurement about the right side of the head was 27.4 cm.; about the left, 28.4 cm. The right foot was 28 cm. in length; the left, 30 cm. The genital development was normal. The thyroid was small. Vision and the eyegrounds were normal. When again seen in 1918, the appearance was essentially the same, except that enlargement of the veins on the right side had gradually increased from the time of the first examination. The next examination was made in January, 1931. He then complained of a condition of the large varices in the right leg and of convulsions that had started about eight years before. The appearance of the face was about as before, but the hands and feet were relatively larger. Some of the measurements (in cm.) were:

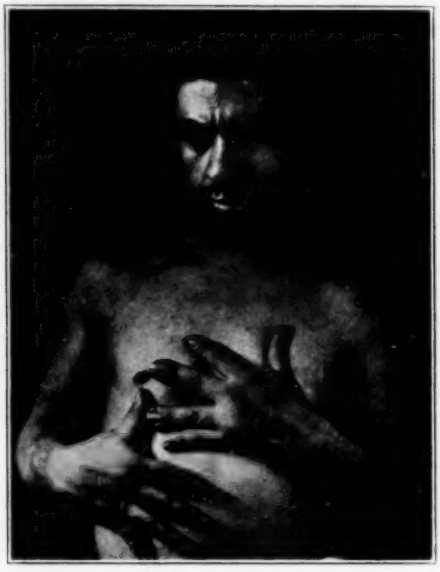


Fig. 1.—Patient with left hemihypertrophy.

	Right	Left
Horizontal arc, glabella to inion	29.5	31.3
Distance of center of pupils from midline	3.4	4.0
Width of nostril	1.0	1.5
Acromion to tip of middle finger	71.0	75.0
Length of middle finger	9.0	12.5
Circumference of first phalanx of middle finger	6.7	8.0
Anterior superior spine to inner malleolus	84.0	88.0
Width of feet	10.0	10.5
Length of feet	28.0	29.0

A roentgenologic report made by Dr. F. H. Squire stated that there was a small sella with almost complete bridging of the anterior and posterior clinoids. There was an area of increased density posterior to the sella, the significance of which was in doubt. There was overlapping between the parietal and occipital bone on the posterior aspect, which suggested an old injury. The hands were rather large. The left hand was larger than the right. The terminal phalanges of the left hand were clubbed, and there was some increase in the distal ends of the metacarpal bones. There were multiple areas of decreased density in the carpals of the hands. The left hand suggested acromegaly.

As is seen in the illustrations, the striking features, in addition to the general left hemihypertrophy, are the disproportionate size of the hands and feet and the prominent varices in the right leg. Twenty years ago, the only feature added to the general hemihypertrophy was the enlargement of the right foot. The cutaneous nevi and pigment spots then existing are common in cases of hemihypertrophy.

In spite of the disproportionate size and growth of the hands and feet it still seems proper to include this case among the congenital hemihypertrophies, along with the classic cases of Stier, Cagiat and others, leaving the question of pathogenesis open. I am at least opposed to considering it as a case of acromegaly because of the existence of the hypertrophy since birth and because of the absence of sellar enlargement and changes in the visual fields. The convulsions are clearly something apart from the essential condition.

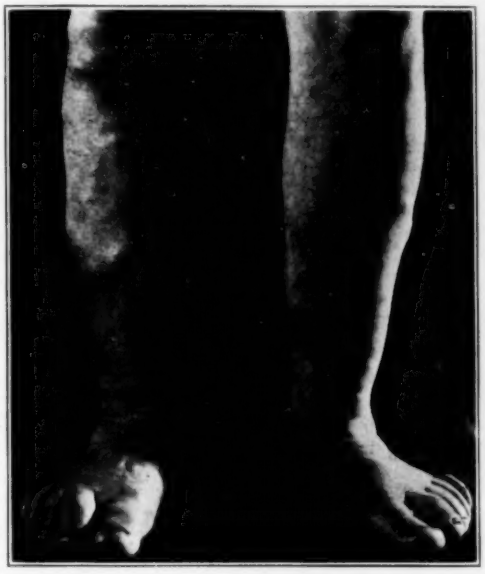


Fig. 2.—The legs of the patient with left hemihypertrophy. There are large varicose veins of the right leg.

DISCUSSION

DR. H. A. PASKIND: This patient has been under observation at the neurologic clinic at Northwestern University School of Medicine since August, 1930. He then complained of convulsions that had been present for the preceding ten years, since the age of 25. The convulsions do not begin with either aura or warning. He suddenly becomes unconscious; there is a short tonic and clonic phase; he does not pass urine or bite the tongue. After the attack he sleeps for a few hours and then feels normal. The attacks occur most often at night, but some have occurred during the daytime. They vary in frequency from two per day to two per week. On one occasion under medication he went for forty days without an attack. At times he has bruised himself during a seizure. He has had no momentary attacks.

Examination showed that the visual fields were normal. The basal metabolic rate on one occasion was +11; on another, +13. Tests for sugar tolerance gave normal results, and the Wassermann reaction of the blood was negative. Examination of the blood showed: 5,800,000 red cells; 6,500 white cells, and 65 per cent

hemoglobin. The urine showed a slight trace of albumin. A roentgenogram showed a normal sella turcica; the left side of the cranial vault was much greater than the right. The skull and the mandible were much thicker on the left than on the right. The skeletal framework of the left hand and foot was considerably larger than that of the right extremities.

DR. PERCIVAL BAILEY: What has been found in the brain in such patients? Has a complete examination of the brain been made in any case? The one thing one might expect to find would be a tuberose sclerosis, and patients with tuberose sclerosis are often epileptic, as this man is. I think that there must be a pathologic condition in the brain.

DR. PETER BASSOE: Only a few cases have been examined post mortem, among them one by Cagiati which was published in the *Deutsche Zeitschrift für Nervenheilkunde* in 1907. No pathologic process such as a tuberose sclerosis was found in the brain.

METABOLISM OF NERVES AND THE PROBLEM OF DEGENERATION. DR. RALPH W. GERARD (by invitation).

Peripheral nerve has been shown to possess a resting and active metabolism of a sort analogous to that of other isolated tissues or of an entire organism. The nerve of a frog at room temperature consumes about 20 c.mm. of oxygen per gram per hour, essentially the same as muscle. Allowing for differences in temperature, the nerve of a rabbit respires from 2 to 3 times as rapidly and the tissue of the brain 70 times as rapidly as nerve. During activity, with a continuous tetanization at 300 shocks a second, the respiration of the nerve of a frog is doubled, but, calculated per single impulse at a lower frequency, it is increased about four times. Therefore, there is definite evidence of a type of fatigue, called equilibration, which appears in the nerve on continued activity. The energy liberated in the form of heat at rest or activity corresponds accurately with the oxygen consumed if the latter serves to oxidize the usual foodstuffs. Although the resting metabolism of nerve and muscle is alike, the increase during activity, weight for weight, is about 8,000 times as great as in muscle. Both the production of heat and the consumption of oxygen remain increased for ten or fifteen minutes after a period of activity. The resting metabolism of nerve depends largely on the oxidation of ordinary carbohydrates, but these do not contribute to the increased metabolism during activity. Studies of phosphorus suggest that the latter may depend on phospholipins. There is also evidence during activity of changes in the creatine-phosphate and in the ammonia content of nerve; these substances seem to play an important rôle in its functioning. When the normal processes are interfered with, the nerve cannot maintain itself in an irritable state; thus exclusion of oxygen leads to failure of the nerve in two or three hours, but if it is not asphyxiated for much longer than this, it recovers promptly when oxygen is again available.

In approaching the question why nerve fibers cut from their cell bodies degenerate, there appear two possibilities: either the normal conduction of impulses is necessary to maintain the nerve in normal condition, or substances reaching the fiber from the cell body, particularly the nucleus, are necessary to its continued survival. Since regular stimulation of the peripheral end of a cut sciatic nerve in dogs hastens rather than delays loss of function, the evidence favors the second alternative. Substances to be oxidized, as well as oxygen, reach the nerve fibers via the blood stream, so that lack of them cannot be the factor involved in degeneration. The oxidations necessary for the survival of cells, however, take place only under the catalytic influence of cell enzymes, probably containing iron. The latter might well be formed only under nuclear influence, so that they must be continually supplied to the peripheral fiber by spreading along it from the cell body. Such enzymes would be expected to disappear more rapidly in active than in resting fibers, and the time for degeneration does decrease in the stimulated

nerve. Therefore, it is suggested that the peripheral nerve degenerates because it is unable to maintain its necessary basal metabolism in the absence of a respiratory catalyst normally reaching it from the cell body by spreading along the axis cylinder. That such a direct spread of substances along the axon can occur is indicated by the known facts of the spread of tetanus toxin and herpes virus.

DISCUSSION

DR. LEWIS J. POLLOCK: There are several schools of thought concerning the treatment for lesions of the lower motor neuron. As Dr. Gerard stated, one of them stresses the necessity for rest in the treatment for anterior poliomyelitis. I wonder whether one can fully accept as the total reason for this the one that Dr. Gerard brought forward tonight. I think that it is of some importance to have an understanding of the abnormal physiologic function of degenerating nerves and muscles, for I think that at present knowledge regarding them is in a more or less chaotic state. Though it is true that at some stages in poliomyelitis rest is an important feature of the treatment, I doubt whether it should be continued throughout the regeneration of the peripheral nerve and muscle. In lesions of the peripheral nerves, comparing those that had been treated by rest and by stimulation with considerable activity, the muscle was found to be considerably reduced so that in some cases in a treated patient with complete injury the muscle might show only 17 per cent loss of total volume of the extremity, whereas in an untreated patient it might show as high as 37 per cent loss. So, in the cases in which treatment consisted of resection and suture there was a return of better function than those in which treatment was not given. The treatment is directed chiefly toward the muscle, but I think that it is well to take note that too prolonged rest need not necessarily be used in these cases, and that it should be used chiefly to prevent the overstretching of fragile muscles.

DR. PETER BASSOE: Speaking along the same line as Dr. Pollock, I remember réading the report of some experiments on animals last year. I. A. Piontkovsky (*Arch. f. Psychiat.* **91**:269, 1930) cut the sciatic nerve in both legs, keeping one leg quiet and using galvanic stimulation on the other. He claimed that the regeneration in the treated side took place in about 50 per cent less time than that in the untreated side.

DR. ARTHUR WEIL: I was interested in Dr. Gerard's remark that after stimulation of a nerve there is an increase in soluble phosphates, the source of which are the lipids of the nerve fibers. Such observations will help to overthrow the old conception that the myelin sheath is something fixed and stable. It, too, has its ever-changing metabolism, and there must be a constant new formation of its main constituents, the lipids. Their decrease in the central nervous system during ether narcosis, together with the ensuing histologic changes of the nerve fibers, is another example of such metabolic lipid changes of the myelin sheath.

DR. RALPH W. GERARD: Replying first to the remarks of Dr. Weil, it is true that there is evidence of liberation of phosphate both by asphyxia and by stimulation, but during the latter there is no deprivation of oxygen. It may well be that the phosphorus comes from phospholipins in myelin. Several able histologists have offered evidence, which seems to me of value, of changes in the myelin during normal activity; this is even more significant than the changes in narcosis.

I can accept everything that was said, except the implication by Dr. Pollock that I thought I was presenting a full explanation of something. As Dr. Pollock pointed out in speaking of the value of stimulating denervated muscle, in this case the muscle cells have not been injured, except by disease, and there is every reason to expect stimulation to keep the muscle in a better state until the nerves are regenerated. Also, in the case Dr. Bassoe mentioned, the nerve fiber is still attached to the cell body, and the regeneration might be facilitated by activity.

THE SENSORY FIBERS IN THE SPINAL NERVES. DR. S. W. RANSON.

After the removal of the abdominal sympathetic trunk on the right side in six cats, from thirty-nine to eighty-four days were allowed for degeneration. The saphenous nerve and the nerve to the vastus medialis, from which all of the sympathetic fibers had disappeared, were stained with osmic acid and by the pyridine silver method. Counts showed that as many myelinated fibers could be recognized in the pyridine silver as in the osmic acid preparations, but in the former there could be seen in addition large numbers of axons without myelin sheaths. This shows that the axons that appear to possess no myelin sheaths in silver preparations are really unmyelinated and not, as Langley suggested, fine myelinated fibers, the sheaths of which are invisible. In the saphenous nerve there are more unmyelinated than myelinated sensory fibers, and they are grouped in bundles of from two to a dozen or more. In the nerve to the vastus medialis these fibers are more scattered and are not nearly so numerous. Most of the somatic sensory unmyelinated fibers, therefore, go to the skin. Smaller numbers go to the muscles. There are good reasons for believing that pain is mediated by these fibers.

DISCUSSION

DR. PERCIVAL BAILEY: Has Dr. Ranson made any study of the sensory root of the fifth nerve? I am interested because of Dandy's recent statement that he can stop the pain in trigeminal neuralgia by cutting the fifth nerve, without any sensory loss in the distribution of the nerve.

DR. S. W. RANSON: There are some observations that have been made on the sensory root of the fifth nerve, which I believe have a bearing on the question that Dr. Bailey has raised. It has commonly been supposed that all of the sensory fibers of the fifth nerve bifurcate within the pons into short ascending fibers that go to the main sensory nucleus and long descending fibers that go to the spinal nucleus. Windle has shown that these are the coarser fibers. There are also finer fibers that turn downward into the spinal fifth tract without bifurcating. It is interesting to note that these fine, nonbifurcating fibers have a more peripheral course in the pons than do the bifurcating fibers. There is also good reason for believing that pain from the face is mediated by the fibers forming the spinal tract of the fifth nerve, and my opinion is that it is mediated by these nonbifurcating fibers. It seems possible that these fibers would be situated at the lower border of the nerve as it enters the pons, which is just where Dandy cuts, and it would not surprise me if by making a section at this border of the nerve close to the pons one would abolish sensibility to pain in the face. But, as I understand it, Dandy does not claim that he abolishes sensibility to pain in the face, but merely cures the trigeminal neuralgia. That I do not understand.

EPILEPSY OF THE ANGIOSPASTIC VARIETY IN MONOZYGOTIC TWINS. D. M. OLKON.

This article was published in full in the ARCHIVES (**25**:1111 [May] 1931).

DISCUSSION

DR. R. P. MACKAY: Can Dr. Olkon tell us how he knows that these capillary changes are not secondary to the convulsive state rather than primary?

DR. D. M. OLKON: I did not say that the vascular spasm was a primary change. At present it is not known what the initial factors are that set the organism in such disequilibrium as the convulsive state. The vascular changes here observed may be secondary to some other dominant factors. My point was that these pronounced vascular changes must be destructive to normal metabolism and may institute a further physiologic imbalance, whatever the initial dynamic stimulus was. That certain types of convulsions, e. g., "genuine epilepsy," are due to deranged neurophysiologic and metabolic processes seems reasonable.

I did not state that the theory of vascular spasm and its relation to convulsions is completely established. One thing seems certain, however, that in these twins vascular tonus was greatly disturbed and progressively increased, and that the generalized convulsions appeared at more frequent intervals. The main purpose of this report was to give a summary of observations made on the microscopic vessels in their relation to the convulsions described in identical twins, and that, clinically, antispasmodic medication in this instance lessened the convulsions and even abolished them for a long period (three years).

PHILADELPHIA NEUROLOGICAL SOCIETY

Regular Meeting, March 27, 1931

JOSEPH MCIVER, M.D., *President, in the Chair*

SURGICAL TREATMENT OF ABSCESS OF THE BRAIN. DR. F. C. GRANT.

No lesion involving the brain requires more judgment and experience in its successful management than an abscess. That an abscess exists may be difficult of proof. Frequently, when its presence seems unquestioned a precise localization cannot be made. Lastly, when the diagnosis of an abscess in a definite area is reached, the decision as to the proper time and method for its evacuation taxes the surgeon's skill. Too often diagnosis and localization are proved correct, only to have the patient die as the result of imperfectly applied surgical measures. An abscess of the brain should be no more difficult to diagnose than a tumor of the brain. Both are space-taking lesions affecting the brain, and in similar situations produce the same symptoms. But the operative mortality from abscess has been hitherto much higher than from tumor. With the purpose of attempting to discover the factors that cause this higher mortality we have analyzed a group of forty cases of abscess of the brain that have passed through the neurosurgical department of the University Hospital in the last eight years.

It becomes immediately apparent that abscess of the brain is not more difficult to localize and diagnose than is tumor of the brain. Thirty-five of the forty abscesses were opened and drained. Three were found at autopsy. In two instances the diagnosis of a tumor was made and an abscess subsequently discovered. These figures make it fairly obvious that inability to localize an abscess is not the reason for the high mortality.

So far as a differential diagnosis between abscess and tumor is concerned, the important fact suggesting an abscess is a history of infection somewhere in the body. Of course, infections of the cranial sinuses are potential factors in the production of abscess of the brain, but one must seek much further than this for the source of possible infection. Abscess of the lungs, an infection on the foot, a trivial cranial trauma occurring more than a year previously, a chronic bronchiectasis, a shrapnel wound of over six years' duration, were found in this series to have been a cause of abscess of the brain. We agree with Foster Kennedy when he says that the only possible way to differentiate between abscess and tumor is by determining whether or not infection has been present. In addition to the purely neurologic symptoms that localize the lesion, when an abscess is present the patient is more toxic, more stuporous, and reacts and responds less readily than might be expected from his symptoms. The temperature is not uncommonly subnormal; there is usually a mild leukocytosis, and we found that percussion over the cranial vault is likely to elicit tenderness on the side on which the abscess is situated.

Considering the surgical treatment for abscess of the brain, I wish to divide our forty cases into two groups of twenty each. This roughly separates the work of the first and second four years, in which these cases were studied. The end

of the first four years coincided roughly with the report of LeMaitre, in France, who stated that by locating the abscess first with a fine needle and then slowly dilating the drainage tract, thus permitting adhesions to form and reducing the chances of meningitis, he had cured sixteen of eighteen patients with abscess of the brain. During the first four years our results had been so far from satisfactory that a change in methods seemed necessary. What factors produce a successful or unsuccessful result in attacking an abscess? Obviously, as we have shown, the introduction of a needle into the abscess cavity and the evacuation of pus may be the simplest part of the problem. There are two factors that must always be given grave consideration: first, the prevention of septic encephalitis around the drainage tract, and second, the development of meningitis.

Frankly, it is our opinion that the cause for the high mortality in abscess of the brain is due to the fact that the abscess is in the brain and for that reason surgeons have allowed themselves to become rushed. Consequently, they have operated at a time in the development of the abscess which they would not have chosen had the lesion been located elsewhere. All of the tissues of the body react in about the same way to infection. The brain reacts more slowly than other organs because the glial elements respond sluggishly to irritation and because there is but a relatively small amount of fibrous tissue present to help form the capsule of the abscess. Therefore, it takes the brain longer to get its defense mechanism under way. No surgeon would operate on an abscess elsewhere until he had permitted time for it to come to a head and ripen. Therefore, why should one attack an abscess of the brain at the earliest possible minute, before encapsulation has occurred and during the stage of septic encephalitis? There are half a dozen autopsy specimens in the collection that show simply a ragged cavity in the brain without the slightest attempt at localization of the pus. These cases, I am sure, were those of patients who were operated on too early and might well have been saved had more time been given to wall off the infection. Not only does delay in these cases enable the brain to erect barriers against the spread of infection but it also tends to reduce the virulence of the organism. Of course, the crux of the situation in suggesting delay in operating on an abscess of the brain is this, namely, that if one delays too long the abscess may spread and rupture into the ventricle or subarachnoid spaces. It is this decision as to when to operate that is all important. How can one tell when the abscess is well encapsulated and ripe for drainage? Lillie has recently stated that he believed that a careful study of the eyegrounds gives the necessary information, that a stationary or subsiding choked disk was evidence that encapsulation had occurred. As only twenty-two of our forty patients showed evidence of pressure in the eyegrounds, it is not certain how practical Lillie's suggestion may be. It is believed that if the patient is in a hospital where the staff is accustomed to dealing with intracranial lesions, and if the surgeon is on the watch for symptoms, waiting is safe.

If the patient gives a long antecedent history of chronic infection with a more or less definite date at which that history commenced, and if there have been obvious signs of an abscess for say roughly six weeks, no further delay is necessary. But if, following an acute mastoid disease, evidence of intracranial involvement suggesting a sudden infection of the brain abruptly develops, operation should certainly not be performed until the acute symptoms have quited down. If immediate operation is done, the brain will be entered during the stage of septic encephalitis and no benefit will result. Little or no drainage will occur, and the trauma accompanying the introduction of the drain will spread the encephalitis.

Another great cause of mortality in abscess of the brain is meningitis. It is not particularly difficult to avoid this complication. The operation must be done in two stages through a small trephine opening. At the time of the first operation, a trephine opening is made over the point at which the abscess has been located. The dura is opened and cotton soaked in antiseptic solution is packed between the dura and the surface of the brain. Twenty-four or forty-eight hours later, after adhesions have formed, the abscess is tapped. So far as introduction of

drainage is concerned a small soft rubber tube is all that is necessary. If there is difficulty in introducing the drainage tube into the abscess cavity after it has once been located, it is much safer to stop and wait for four or five days and then attempt to introduce the tube.

This series of forty cases has been divided into two groups of twenty each for the sake of comparison. In the first group, in every case the operation was performed promptly, usually in one stage. Only two of these patients recovered. In the second group the operation was delayed as much as possible. The operation was performed in two stages whenever feasible. No great effort has been made to introduce drainage into the abscess if that seemed to involve the surrounding brain in undue trauma. Fourteen of the twenty patients in the second group recovered. It is further interesting to note that whereas the time from the onset of symptoms to operation in the first group averaged between three and three and a half weeks, this period in the second grouped averaged just under nine weeks. We believe, therefore, that an abscess of the brain is not necessarily a surgical emergency. Plenty of time can be permitted for arriving at the conclusion that an abscess of the brain is the real, underlying lesion and locating it with the utmost possible accuracy. At the end of that time a trephine opening can be made over the point at which the abscess is suspected to lie, and the subarachnoid space packed off. Once this is done, it is possible to tap the abscess at any minute without danger of meningitis. Even then, provided that the patient shows no clinical symptoms suggesting urgency, he can be advantageously kept under close observation for a week or more before the abscess is tapped. If this is done and if the brain is allowed to marshall all its forces to combat the infection, and if at the time of tapping undue trauma of the surrounding brain does not occur, there is no real reason why cure should not be obtained in a large percentage of these solitary abscesses of the brain.

Ocular Manifestations of Tumor of the Occipital Lobe. Presented by Dr. William Duane, Jr.

This paper will be published in full elsewhere.

Two Cases of Tumor of the Brain with Homolateral Paralysis. Presented by Dr. Reed Harrow.

This paper will be published in full elsewhere.

Adamantinoma of the Pharyngeal Duct. Presented by Dr. C. H. Frazier and Dr. B. J. Alpers.

This paper will be published in full in a later issue of the Archives.

BOSTON SOCIETY OF PSYCHIATRY AND NEUROLOGY

Tracy J. Putnam, M.D., *Secretary*

Three Hundred and Ninety-First Meeting, March 19, 1931

Abraham Myerson, M.D., *in the Chair*

Myelotomy in the Treatment for Syringomyelia. Dr. Tracy J. Putnam and Dr. Donald Munro.

In 1926, Professor Puusepp, of Dorpat, reported two cases of syringomyelia in which he had opened the cavity surgically with relief of symptoms. Similar operations had been performed previously, usually with good immediate results

Since then, about forty more cases have been reported, and improvement has been observed in the great majority. We have operated in two cases.

Case 1.—J. B., a man, aged 55, complained of pain in the left arm, requiring morphine, with weakness and tingling. Examination showed atrophy of the trapezius and sternocleidomastoid muscle and of all of the muscles of the left arm, Horner's syndrome on the left side and exaggerated reflexes in the left arm and leg. The Babinski reflex was positive on the left. There was hyperesthesia for pain and heat in the left arm and leg, with hypesthesia for light touch over the same area. Hypesthesia for pain and heat was present in the right leg and arm.

A spinal block was demonstrated by lumbar puncture and there was a partial arrest of ascending iodized poppy seed oil 40 per cent at about the eighth dorsal vertebra.

The diagnosis was syringomyelia with block.

On Nov. 4, 1928, with the patient under ether anesthesia, the laminae of the fourth, fifth, sixth and seventh cervical vertebrae were removed. Two fusiform enlargements of the cord were exposed, one at the fourth cervical vertebra and the other at the sixth cervical vertebra. There was thickening of the arachnoid. The lower enlargement was split in the midline posteriorly, and about an ounce (29 cc.) of xanthochromic fluid escaped under pressure. The walls were black and discolored. The upper enlargement was incised and found to be solid.

The patient recovered rapidly and easily from the operation. He was partly relieved from pain and did not require morphine, but the disability and physical signs were unchanged. He was discharged to Long Island Hospital, where he died on April 11, 1929. An autopsy was not performed.

Case 2.—J. M., a man, aged 24, was admitted to the neurologic service of the Boston City Hospital on Sept. 18, 1930. He had had attacks of unconsciousness between the ages of 7 and 19. He had had staggering since childhood, especially with the right leg. There was scoliosis. For one year, he had had stiffness and weakness of the right arm and leg, and was unable to raise the right arm above the head. He burned his fingers with cigarets without knowing it. He had great difficulty in walking. Vision was poor.

Examination revealed the following symptoms: atrophy and weakness of the left shoulder and both hands; bilateral Babinski sign and ankle clonus; spastic gait; sensory changes consisting chiefly of loss of sense of temperature in both arms and the left side; bilateral paracentral scotoma. Lumbar puncture showed 9 cells at one time in the fluid; at another time, the protein content was 83, with a pressure of 230 and a small reservoir but no block.

A diagnosis of syringomyelia was made, and roentgen treatments were given for four months. During this time the condition grew steadily worse. He accordingly entered the neurosurgical service on Jan. 7, 1931, for an operation.

On January 19, with tribrom-ethylalcohol and local anesthesia, a laminectomy of from the third to the seventh cervical vertebrae was performed. The arachnoid was thickened, and the pia was more vascular than normal. The cord was swollen so that it filled the entire canal over the area exposed. It was punctured in the midline, and 2 cc. of fluid containing 28 mg. of protein was aspirated. The incision was then made in the midline, allowing the escape of about 100 cc. of fluid under pressure. The incision was lengthened to 15 cm. The cavity exposed was lined with yellow tissue and appeared to communicate with the ventricles. The thin wall of the cyst lay in loose longitudinal folds. The wound was closed without drainage.

The patient made a good operative recovery. The sensory disturbances rapidly decreased, until only a hypesthesia for temperature remained in the right side of the chest, the left hand and both feet. Spasticity decreased, and walking improved. The muscles of the hands and forearms regained their contour and strength. The patient is now seeking work. Roentgen treatments are being continued.

It is probable that the incision of the cavity has no effect on the gliosis. On the other hand, roentgen treatment, which is the standard therapeutic procedure, probably has no effect on the pressure within the cyst. The two methods supplement each other.

The operation does not appear to be a particularly dangerous one in practiced hands. For the present it should probably be reserved for cases in which there is pain, spinal fluid block or disability, and for cases resistant to roentgen treatment. It may prove to have a value in preventing the progression of symptoms, but this remains to be demonstrated.

DISCUSSION

DR. D. GREGG: Were there changes in the visual fields?

DR. E. W. TAYLOR: You spoke of incising the central canal and stated that this canal was much enlarged. Should not a sharp distinction be made between syringomyelia and so-called hydromyelia? Ordinarily, in adult life the spinal canal is obliterated and is not dilated in the syringomyelic process. The origin of syringomyelia is always outside the spinal canal and ordinarily has no connection with it. Therefore, it is desirable to make a somewhat sharp distinction between the exceedingly rare hydromyelia consisting of a dilatation of the central canal and syringomyelia which is an entirely different process beginning in the dorsal gray matter and thence extending without invading the central canal. It would be interesting to know whether in the case under discussion we are dealing with a true syringomyelia or a hydromyelia. Pain was mentioned as a rather conspicuous symptom. My impression is that pain is a rare accompaniment of syringomyelia, as is usual when the lesion is within the spinal cord and does not directly involve the roots of the nerve. It is conceivable, however, that pressure might bring about pain. Attacks of fainting were mentioned. Were these attacks epileptiform or syncopal? An interesting point is the changes in the eyegrounds in the patient presented. I remember a case in which toward the end of a very painful illness, in which the spinal cord was primarily involved, a pronounced choked disk developed. Necropsy showed a tumor almost filling the subdural space and reaching as far as the cervical enlargement. At the time it was suggested that this blocking off of a possible escape for cerebrospinal fluid might have been instrumental in producing the increased intracranial pressure. The brain showed no evidence of a tumor or any other pathologic lesion, except what was apparently a secondary hydrocephalus. Other similar cases have been described. It is interesting to note the high degree of ataxia in Dr. Putnam's patient. Of course, spasticity is almost always present, and often it is greater on one side than on the other, but in my experience ataxia is an unusual condition.

DR. D. MUNRO: It would no doubt be advisable to extend our diagnostic accuracy. It is of value to be able to decide exactly where one is going to incise the cord. In one of my cases iodized poppy seed oil was used both from above and from below the seventh and eighth dorsal vertebrae. The operation was performed in the cervical region. No attention was paid to the ascending iodized poppy seed oil, as this was in the dorsal region. The patient had relatively slight relief from symptoms. It is not inconceivable that the remaining symptoms may have been caused by the untreated second cyst in the dorsal region. In proposed surgical intervention it should be not only advisable but also necessary to inject iodized poppy seed oil from above and below. The question of multiple cysts must be seriously considered and, if possible, accurately located.

DR. J. B. AYER: I have usually found roentgen therapy satisfactory in preventing the progress of syringomyelia. One patient whom I have followed up since 1925 has shown no continuous progress in symptoms. For a time he showed bulbar symptoms which regressed with further roentgen treatment. But I wish to speak particularly of the case of Dr. Mixter's cited by Dr. Putnam. The boy presented looks enough like him to be his twin brother. In Dr. Mixter's case an operation was performed because of the presumptive diagnosis of intramedullary glioma. When the cord was split posteriorly, there was a gush of a considerable amount of fluid; it was clear and did not contain an increase in protein. Unfortunately the external wound never healed; meningitis developed, and the patient died. Postmortem examination performed by Dr. Kubik showed a

typical syringomyelia with several cavities. I believe, as does Dr. Putnam, that an operation is unlikely to retard the progress of syringomyelia, and I should hesitate to advise operation except in a case of block.

DR. F. FREMONT-SMITH: In this case, at each of several lumbar punctures, jugular compression produced a prompt rise in the pressure of the spinal fluid; at operation, however, the subarachnoid space was completely obliterated. The fluid from the cyst was clear and colorless, with a very low protein content that resembled ventricular fluid. The explanation is that even though the cystic cord is distended so that the subarachnoid space is obliterated, it will transmit the fluid wave produced by jugular compression; that is, the raised intracranial pressure compresses the upper part of the cystic cord, and this causes distention of the lower part of the cystic cord, which raises the pressure of the spinal fluid below the block. This means that subarachnoid block resulting from a distended syringomyelic cavity cannot always be demonstrated by the Queckenstedt test. This may explain why block has been so rarely reported in this disease. It also suggests that one ought to resort more often to injections of iodized poppy seed oil in these cases, as Dr. Munro has suggested.

DR. T. J. PUTNAM: The patient says that he sees somewhat better. The visual fields show no change. Many of the attacks of fainting were epileptic. The cavity sometimes does and sometimes does not communicate with the central canal, and the canal may or may not communicate with the ventricle. In the two cases reported, the lining of the cavity consisted of dark, yellow, glial tissue. Presumably, the cases in which the cavity is small or absent are the ones that respond most readily to roentgen treatment. Cases in which there is pain, apparently occurring from an involvement of the posterior horn, are unusual, but they are naturally very prominent in the surgical literature. The condition in the eye was retrobulbar neuritis with optic atrophy rather than papilledema. I have not encountered in the literature any instances in which there was increased intracranial pressure, though dilatation of the ventricles has been reported. We have also had a case in which irradiation has improved the condition remarkably, but in the cases here reported the condition of the patient was worse following irradiation; this occurred in 33 per cent of the cases collected by Delherm and Morel-Kahn. The fluid is sometimes xanthochromic and sometimes colorless. Block occurred in a large proportion of the cases reported prior to the publication of Puusepp's paper, but in few of the cases reported since; however, relief was secured in most of them.

INTERNAL JUGULAR VENOUS PRESSURE AND ITS RELATIONSHIP TO THE PRESSURE OF THE CEREBROSPINAL FLUID. DR. ABRAHAM MYERSON and DR. JULIUS LOMAN.

This paper will be published in full in a later issue.

DISCUSSION

DR. F. FREMONT-SMITH: In 1920, Becht, using cats, was the first to point out that the pressure of the spinal fluid is intimately dependent on venous pressure and almost independent of arterial pressure. Weed found that the pressure of the spinal fluid in cats is greater than the venous pressure in the dural sinuses. This agrees with Dr. Myerson's observations in man, that the pressure of the spinal fluid is greater than that in the internal jugular vein, for the pressure in the jugular vein must be less than that in the dural sinuses. In the smaller cerebral veins, however, the pressure must be greater than that of the spinal fluid, for if the pressure within these thin-walled vessels, lying in the subarachnoid space, were less than that of the spinal fluid, the veins would be compressed. Claude and Lamache have measured venous pressure in the arm simultaneously with pressure of the spinal fluid. Their observations are analogous to those reported by Dr. Myerson and Dr. Loman, namely, that an intimate relationship exists

between venous pressure and the pressure of the spinal fluid. In cardiac decompensation, both venous and spinal fluid pressures were elevated. This new technic of measuring internal jugular venous pressure offers a new approach to the study of intracranial pressure and circulation in man.

DR. GREGG: Would this bring up the question of higher pillows for people who cannot sleep?

DR. A. MYERSON: It is of interest that a steady, high arterial pressure has no marked effect on the pressure of the spinal fluid. Nevertheless, the arterial pressure rises and falls with change in posture, straining and the respiratory cycle, just about the same as the spinal fluid and venous pressure. We studied the pressure in a carotid, the spinal fluid and a jugular vein in a patient with dementia praecox. By squeezing the thorax, the intrathoracic pressure was changed, and there was a corresponding rise in arterial, venous and spinal fluid pressure. When abdominal compression is used, there are probably two direct effects: (1) a compression of the inferior vena cava and (2) an increase in intrathoracic pressure. As a result, there is a rise in the pressure of the spinal fluid and a rise in jugular venous pressure. I do not know whether or not the compression of the lumbar veins by abdominal pressure is a factor in the rise of the pressure of the spinal fluid. We are certain that the technic of jugular puncture combined with spinal fluid puncture and occasionally combined with arterial puncture offers a clinical approach to intracranial dynamics, such as is afforded by no other clinical measure.

THE RESULTS OF THE TAKATA-ARA TEST IN FOUR HUNDRED CASES: A PRELIMINARY REPORT. DR. RALPH W. DAFFINEE.

In 1926, two Japanese investigators, Takata and Ara, described a colloidal type of reaction in spinal fluid which they considered specific for neurosyphilis and of great value in segregating pathologic fluids of various sorts. Since that time this test has been given trial by numerous investigators, particularly in Germany and Italy, mostly in connection with psychiatric clinics.

Takata and Ara reported 146 cases, 40 of which were definite neurosyphilis. Of their so-called normal patients, 3 per cent gave a false positive reaction, while the Wassermann reaction of the spinal fluid was negative in all. In the cases of neurosyphilis, they obtained 97.5 per cent positive reactions. They concluded that their reaction was equal to the Wassermann and perhaps was more sensitive in cases in which treatment had been given. It was of more value as a check on the Wassermann test than the other usual laboratory tests.

Shortly after this, Knigge reported the results of 200 tests. He came to the conclusion that it was not specific for syphilis, and that it was of more value in psychiatric than in general neurologic cases. Bluhm, as a result of his study in 200 cases, thought it to be a worthwhile test. Munzer, who reported 100 cases, considered it valuable in separating syphilitic from nonsyphilitic cases. Jakobsthal and Joel showed a 92.1 per cent agreement with the clinical diagnosis. Meyer, studying his cases in entirety, found it to be somewhat less reliable than the Wassermann reaction. The Takata-Ara reaction, however, was of more significance in established cases of neurosyphilis, especially in those in which vigorous treatment was given. He found many false positive reactions in nonsyphilitic fluids.

The test is carried out as follows: To 1 cc. of spinal fluid, 1 drop of 10 per cent sodium carbonate solution is added. Takata's reagent is made by the mixture of equal parts of 0.5 per cent mercuric chloride and a 0.02 per cent solution of basic fuchsin; 0.3 per cent of this mixture is added to the spinal fluid; the whole mixture is shaken, and then is allowed to stand. Readings are made after fifteen minutes, six hours and twenty-four hours. A normal fluid will give a bluish-violet clear reaction, with only minimal flocculation after twenty-four hours. A syphilitic fluid gives a definite purple precipitate, with a clear, supernatant fluid. The meningitic reaction is rose red and clear. In addition, there are a certain number of mixed reactions, usually reddish with a pink precipitate.

This reaction is explained on a colloidal basis. In the presence of the small amount of alkali, the mercuric chloride forms mercuric oxide. The fuchsin present is adsorbed by the crystals of mercuric oxide, giving a bluish-violet color to the fluid. According to Takata and Ara, the stability of this suspension may be broken up in two ways, giving the two types of pathologic reaction. In neurosyphilis, the changes seem to be degenerative, with the production of globulin, whereas in the inflammatory conditions, both albumin and globulin are produced.

In the syphilitic fluids, the presence of the globulin causes a lowering of the stability of the colloid suspension and the adsorption of the dye is increased, so that the particles become visible; a heavy precipitate is formed, which in the strongly positive cases sinks to the bottom of the tube, leaving the supernatant fluid colorless.

In fluids in which an inflammatory process is at work, the increased albumin content causes an increased stability of the colloid suspension; adsorption is inhibited, and the fluid takes on the pink color of the fuchsin. The presence of blood serum in spinal fluid will give a similar reaction.

It has also been noted that a syphilitic reaction can be changed into a meningitic one by the addition of acid, and that a meningitic reaction can be made normal by adding an excess of alkali. The question naturally arises, therefore, as to the part played in the reaction by the p_H of the spinal fluid.

Our tests comprised about 400 cases taken at random from fluids sent to the spinal fluid laboratory of the Massachusetts General Hospital for routine examination. For purposes of classification, we have separated them into six groups: (1) cases in which neurosyphilis has been diagnosed; (2) cases in which neurosyphilis is suspected; (3) cases of syphilis with no signs or symptoms referable to the central nervous system; (4) neurologic cases; (5) medical cases; (6) cases without definite diagnosis.

We have compared the results of four tests: the total protein content, the colloidal gold reaction, the Wassermann reaction of the spinal fluid and the Takata-Ara reaction. In addition, Miss Grezebieniowska has incorporated the results of 90 modified colloidal benzoin reactions. In practically all cases, this test showed a curve identical with the colloidal gold reaction.

In the first group, that is, the cases of definite neurosyphilis, there were 65 patients, 45 of whom had or were having active treatment. In these cases we found 69 per cent positive reactions to the Takata-Ara test and 70 per cent positive reactions to the Wassermann test of the spinal fluid. The colloidal gold reaction was more sensitive, showing 81 per cent, while the total protein was above 45 in only 49 per cent. In a comparison of the four tests, the Takata-Ara showed a majority agreement (that is, it agreed with two of the other tests) in 90 per cent of the fluids, while the Wassermann test of the spinal fluid showed a majority agreement in only 81 per cent.

In the second group, consisting of patients with clinical signs pointing to neurosyphilis, there were 5 cases. The Wassermann reaction of the spinal fluid was negative in all; the total protein content was below 45 in all; the colloidal gold reaction was weakly positive in 1; the Takata-Ara reaction was normal in 3, meningitic in 1 and faintly syphilitic in 1.

There were 48 cases of systemic or latent syphilis, in 39 of which a normal spinal fluid was found. In the remaining 9, either the Wassermann reaction of the spinal fluid was positive or a positive reaction to the Takata-Ara test was elicited. In 7 of these, an abnormal colloidal gold curve was found; in 6 a positive reaction to the Takata-Ara test; in 5 a positive Wassermann reaction of the spinal fluid, and in 1 an increased total protein content. The positive reactions to the Takata-Ara test showed a majority agreement in 4 cases; the Wassermann reaction in the spinal fluid in only 2 cases.

There were 155 cases in which a neurologic diagnosis was made, in none of which was there a positive Wassermann reaction of the blood or a history of syphilitic infection. The diagnoses of the conditions in this group included all

of the common neurologic conditions and many unusual ones. In 4 cases the fluids were grossly bloody, and could not fairly be included. Of the remainder 86, or 56 per cent, were entirely normal.

I shall not discuss the various conditions that produced pathologic reactions. Meningitis, tumor of the brain, tumor of the cord, multiple sclerosis and polyradiculitis gave consistently positive reactions, usually of a mixed type.

Of the fluids showing an abnormal reaction, 53 had a moderate or a marked increase of total protein. Of the 12 fluids in which there were low total protein and positive reactions to the Takata-Ara test, 2 showed a position reaction to the Wassermann test of the spinal fluid and an abnormal colloidal gold curve.

There were 54 fluids from patients from the medical wards; in 2 of them the spinal fluid gave a positive reaction to the Wassermann test, with no corroborative evidence for disease of the central nervous system. In 12 cases an abnormal Takata-Ara reaction was elicited. One of these was a case of morphinism, and 6 cases showed an increase of the total protein. In the 5 remaining cases, the fluids were from patients with no other signs or symptoms of syphilis of the central nervous system.

In 34 cases, no clinical diagnosis could be made with certainty. In 2 cases the spinal fluid gave a positive reaction to the Wassermann test; both were corrobated by the colloidal gold curve and the Takata-Ara test. In 16 cases, the Takata-Ara test gave abnormal results. In 11 of these, a total protein content of more than 45 was found. In 14 of these 16 cases, the colloidal gold curve was also abnormal.

In summarizing, 361 tests were checked by the examination of clinical records and laboratory tests. Of these, 211 gave a normal reaction to the Takata-Ara test. There were 150 abnormal reactions, 27 of which were accompanied by no other abnormal condition of the spinal fluid or clinical symptoms.

Therefore, it must be deduced from these facts that the reaction of the Takata-Ara test (and the Wassermann reaction of the spinal fluid as well) is not reliable as an isolated phenomenon. It is not so specific for neurosyphilis as the Wassermann test. It is as sensitive as, if not somewhat more sensitive than, the Wassermann test of the spinal fluid in following the progress of cases of neurosyphilis in which treatment has been given. The Takata-Ara test finds its greatest agreement with the colloidal gold curve.

In fluids from nonsyphilitic persons, the reaction seems to be unreliable in cases in which there is an increased total protein content. The presence of blood or antibacterial serum also upsets the reaction.

The advantage of the test lies in the fact that it is easy to perform and not difficult to interpret when used with clinical observations and routine laboratory procedures. It can be carried out in the laboratory of the practicing physician, without complicated apparatus or elaborately prepared solutions.

In the hospital laboratory it adds nothing to the facts brought out by the colloidal gold curve, and loses value by the fact that it requires a whole cubic centimeter of spinal fluid. I believe that it is a valuable corroborative test, and that in 90 per cent of cases, at least, an abnormal reaction represents an abnormal condition of the spinal fluid.

DISCUSSION

DR. J. B. AYER: Has Dr. Daffinee found the test of particular value in pediatrics? About six years ago, Miss Cockrill carried on an investigation in our laboratory comparing colloidal gold, benzoin and mastic tests. She came to the conclusion that the tests with benzoin and gold were the most accurate, but that the test with colloidal gold showed somewhat more than that with benzoin; hence we have continued to use it. If the Takata-Ara test proves as accurate on further study as is indicated in the present series, the simplicity of the test would commend itself for use in offices for which the test with colloidal gold is too complicated.

DR. RALPH W. DAFFINEE: We were primarily interested in cases with weakly positive Wassermann reactions and no clinical evidences of syphilis. The reaction fills the need for an easy and rapid test on the spinal fluid which can be recommended as an office procedure. The fluids that I have shown gave as definite a reaction within half an hour as they do now. Fluid from a patient with dementia paralytica reacts almost instantaneously. The solutions of fuchsin and sublimate can be put up by any pharmacist and are stable for at least several months. Takata's reagent, on the other hand, must be freshly mixed from these two solutions.

Book Reviews

ZUR PATHOLOGIE DER DEMENTIA PRAECOX. GASTROINTESTINALE STÖRUNGEN, IHRE KLINISCHE UND ÄTIOLOGISCHE BEDEUTUNG. By DR. PAUL J. REITER. Price, 18 marks. Pp. 216. Copenhagen: Levin & Munksgaard. Leipzig: Georg Thieme, 1929.

A review of the old literature of the period when one could hardly speak of psychiatry as a science brings out the fact that dyspeptic symptoms were frequently observed in mental cases by the older writers. This fact was recognized by Griesinger, although he did not consider it essential, and warned against the theory of "kopropsychiatry." The oldest investigations are concerned mainly with the gastric pathology, that is, abnormalities of the gastric secretion and motility.

With regard to disorders in psychotic patients, Reiter refers particularly to the work of Buscaino, Cotton and Lingjerde. Buscaino has frequently found inflammation of the small intestines in dementia praecox, amentia and postencephalitic conditions in postmortem examinations. Cotton's roentgenologic studies have shown ptosis, atony and more or less pronounced dilated areas in the large intestines. The postmortem examination confirmed these observations. Moreover, they revealed inflammatory processes and atrophied regions, with an extremely thin wall.

Reiter finally presents a comprehensive review of the literature concerned with pathologic indicanuria, which he considers, in accordance with general opinion, to be a sign of intoxication produced particularly by alterations of the upper portion of the small intestines. The presence of indicanuria in a psychotic patient would justify considering the psychosis as an enterotoxic condition. Indicanuria has been found by Lingjerde to be combined with urobilinuria in a certain number of mental cases. He made extensive studies on urobilinuria and bilirubinemia in 213 schizophrenic patients among other psychotic patients. In schizophrenia a pathologic urobilinuria was found almost constantly in the phase of the psychotic process "assumed to be active," but not in other phases of the diseases. Lingjerde also found a rise of bilirubin in the blood in 75 per cent of 100 schizophrenic patients. These clinical signs of functional insufficiency of the liver were confirmed by postmortem examinations, so far as the majority of cases presented "pronounced macroscopic alterations in the liver." The liver insufficiency may create, in Lingjerde's belief, a favorable ground for intestinal autointoxication, and the consequent indicanuria which, as already mentioned, has been found in many cases to be combined with urobilinuria.

The author's investigations comprise: 1. Functional studies in (*a*) dementia praecox (79 cases); (*b*) control cases (55 cases), including manic-depressive psychoses (38 cases), psychopathy (4 cases), epilepsy (4 cases) and organic psychoses (9 cases, of which 6 were dementia paralytica). 2. A study of motility disorders in 14 schizophrenic patients. 3. Postmortem examinations in 23 schizophrenic patients.

In the selection of cases Reiter, in accordance with Kraepelin's conception of dementia praecox, considered the following three main groups: (*a*) catatonia, (*b*) hebephrenia and (*c*) paranoid dementia. A distinction was made also between recent and old cases; a duration of the psychosis for three years was accepted as the borderline between these two groups.

The functional studies are concerned with the secretion and motility of the gastro-intestinal tract, with functional tests of the liver and pancreas and with the quantitative determination of indicanuria, used as a test of intestinal autointoxication. Roentgen examination of the gastro-intestinal tract was made in certain cases only. In a number of patients the size of the pupils was noted every morning for a month. The pulse rate and temperature were followed in 115 schizophrenic patients, also for a month.

In cases which came to autopsy, the different segments of the gastro-intestinal tract, the liver, the mesenteric ganglia and, in some cases, the pancreas and the kidneys were examined microscopically.

Results Obtained in the Control Cases.—1. The gastro-intestinal function was investigated by the usual functional tests in 38 manic-depressive patients. 2. Hyperacidity and gastric ulcer were frequently found in depression. 3. In more than half of the patients constipation was observed; it was equally distributed between manic patients and those with melancholia. 4. Deficient digestion of carbohydrates was noted in 47 per cent of the 38 cases; in 18 per cent, the abnormal fermentation attributed to disorders in the external secretion of the pancreas was accompanied by diarrhea. 5. A slight increase of the colonic catalase was rather frequently found; it was generally associated with occult blood in the stools and fermentative dyspepsia. 6. In a series of cases, indicanuria beyond normal limits was found in association with the intestinal disturbances. 7. Pathologic urobilinuria was not infrequently observed. 8. The outstanding disorders, which in the author's belief are likely to have a bearing on manic-depressive psychosis, are the following: (*a*) periodic hyperchlorhydria in melancholia; (*b*) relatively frequent occurrence of gastric ulcer; (*c*) frequency of fermentative dyspepsia. 9. The remaining 17 control cases (4 psychopathic patients, 4 epileptic patients, 6 patients with dementia paralytica, 1 with Wilson's disease, 1 with Alzheimer's dementia and 1 with presbyophrenia) have not shown features worth considering.

Dysfunction of the Gastro-Intestinal Tract in Schizophrenia.—1. Gastric Disorders: Hypersecretion, particularly after eating, was found to be rather intermittent in the beginning of the psychosis, and became more constant as the psychosis continued, finally receding more or less. The hypersecretion proved to be associated with a tendency to low acidity and heterochylia, and in typical cases with hypochlorhydria and achylia. In certain recent cases, hyperchlorhydria was observed for a short time. The secretion of pepsin showed first a rise, then varied, and finally changed to subnormal. There was also a noticeable tendency to a delayed evacuation, which, however, was not often very pronounced.

2. Intestinal Disorders: In many cases there were symptoms of dyspepsia of the small intestines (muscle fibers in the stools and abnormal digestion of carbohydrates). Yet the striking feature was the frequent discovery of occult blood and an increased catalase in the stools; these abnormalities were in most cases accompanied by intestinal sluggishness, particularly in those of a recent psychosis; in the old schizophrenic patients the evacuation was found to be rather irregular, and often diarrhea had taken place. Not infrequently, inflammatory processes were observed, and proved fatal in some cases. In association with these troubles indicanuria was often found. It was thought that in certain patients a correlation could be established between the indicanuria and the phase of the disease. Finally with regard to liver function, signs of insufficiency were found, corroborating the observations made by other investigators. In concluding the summary of the results obtained, Reiter emphasizes the following two outspoken abnormalities: Gastric hypersecretion (with low acidity) and signs of intestinal inflammation.

The Cause and Nature of the Gastric Disturbances in Schizophrenia.—The syndrome consisting of hypersecretion, delayed evacuation and occult blood in the feces suggests a gastric ulcer. Roentgenologic examination in 14 cases of schizophrenia did not, however, reveal signs of ulcer. Neither did the postmortem examination substantiate the clinical impression, as in only 1 of 9 cases was a bleeding pyloric ulcer found. Thus the investigation in 23 cases with regard to gastric ulcer did not show a higher frequency of this disease in schizophrenic patients than in normal persons. Reiter also discusses the question as to whether mechanical irritation by food, on account of deficient mastication or irritation by drugs, might possibly be the cause of the gastric disorders. The analysis of the cases leads him to conclude that these factors were not operative. Neither does he believe that vegetative disturbances could explain the gastric disturbances satisfactorily. In his opinion they would be due to gastritis. This conclusion is based (1) on clinical observation, that is, the evolution of the hypersecretion and the secretion of acidity; (2) mainly on the anatomicopathologic investigations.

Of 6 patients with functional gastric disorders, 5 showed distinct signs of gastritis. Furthermore, in each of 23 patients who were not investigated clinically, gastritis was found at postmortem examination. Reiter, as already mentioned, has also frequently observed chronic enteritis and colitis in his schizophrenic patients. The consistency of these gastro-intestinal disorders makes him believe that they are closely related to the etiology of the psychosis. The inflammation of the intestines, which he considers the primary and outstanding drug disorder in dementia praecox, would cause gastritis through blood intoxication. An experimental study in dogs that were provided with a gastric fistula, so that the secretion could be followed, has shown that injections of the exotoxins of the feces of patients with dementia praecox provoked secretory disorders similar to those which he observed in his patients with gastritis. These observations would corroborate, in Reiter's opinion, the assumption that the enterocolitis is the primary disorder and the gastritis secondary. They also would suggest that the enterocolitis may be related to the disorders of the brain as well, as it appears to be related to the gastric disorders.

Anatomicopathologic Investigations on the Alimentary Tract in Dementia Praecox.—These investigations, carried out in 23 cases, have shown gastro-enteritis in every case. The alterations of the stomach were found to be of two kinds: (*a*) atrophic proliferative inflammation with a thickened mucous membrane; hyperemia, infiltration with round cells, and thickness of the muscular layer; (*b*) more often, atrophic inflammation with a thin, contracted and atonic wall; the infiltration of the mucous membrane with round cells goes hand in hand with the the overdevelopment of the connective tissue.

The enteritis may manifest itself by alterations ranging between simple hyperemia, edema and diphtheritic ulcerative processes. The inflammation was generalized in some cases, and in others was limited to single segments in the following order of frequency: cecum, transverse colon, duodenum, sigmoid, ileum and jejunum. The enteritis is often accompanied by mesenteric adenitis and pathologic modifications in the liver: fatty liver and more or less pronounced signs of hepatitis.

On the basis of these postmortem observations and the clinical observations already recorded, the author assumes that the enterocolitis in dementia praecox is likely to be primary. The gastro-intestinal evolution *quoad vitam* may be favorable. Not infrequently, however, the chronic process turns into an acute one with a malignant, uncontrollable diarrhea, and often with a fatal issue. Such a malignant evolution is met with often, so that enterocolitis would present, in the opinion of the author, perhaps the most frequent cause of death of patients with dementia praecox.

The Correlation Between the Gastro-Intestinal Disorders and the Psychosis: The Theory of Infection in Dementia Praecox.—It is in the United States that the theory of the rôle of infection in mental diseases has been developed and applied practically to treatment in an extremely large measure. The theory has been applied by Cotton, its proponent, not only in dementia praecox, but also in the so-called "functional" psychoses. The latter (epilepsy, manic-depressive psychoses, schizophrenia) would be of septic origin; other factors would hardly deserve serious consideration. The author disagrees with Cotton's overemphasis of the rôle of the teeth as septic foci and attributes much more significance to the inflammatory processes of the alimentary canal. Recognizing the importance of hereditary predisposition, which in a given person may be specific to a certain type of psychosis, Reiter also believes that there must be a definite noxa which would have an affinity to the substratum of the schizophrenic predisposition, namely, to certain regions of the brain. The noxa would induce chemical or anatomic alterations directly responsible for the disease.

Considering the theory of the rôle of the gastro-intestinal infection in psychoses as a working hypothesis, Reiter attempts to evaluate in the light of this theory the significance of other systemic disorders. A review of the literature concerned with theories of the rôle of heredity and the endocrine organs in mental diseases leads the author to conclude that these theories have proved to be inade-

quate, so far as they assume that an inborn predisposition or an altered glandular function may be the only potent factors in inducing schizophrenia. If heredity plays an extremely important rôle, exogenous factors are of no minor significance. Endocrine disturbances have been found in schizophrenic patients, and anatomic examinations have brought out pathologic modifications in various endocrine organs. However, nothing specific and consistent has been found which would justify the conception that dementia praecox is an endocrine disease. On the other hand, the clinical neurologic observations in catatonia (catalepsy, hypertonia, contractures and parkinsonism), in addition to the other systemic disorders, suggest that dementia praecox is an exogenous organic psychosis presenting features strikingly similar to those of the Bonhoeffer type of psychosis. Anatomicopathologic studies seem to corroborate this view, as they show pronounced modifications, if not specific ones, particularly in the central ganglia.

Among other symptoms that would support the theory of infection, Reiter points to the abnormal temperature; in his experience, 75 per cent of schizophrenic patients had temperatures above normal. The most probable cause would be gastro-enteritis, which has so frequently been proved to affect schizophrenic patients. The theory of infection would also find support in the anatomicopathologic observations. In this respect, Reiter refers particularly to the studies of Buscaino, Josephy and Marburg, among many other investigators, studies which suggest that dementia praecox is a "parenchymatous degenerative disease on a toxic basis."

In the light of the bibliographic data reviewed and his personal studies, Reiter presents the rôle of gastro-intestinal infection in the etiology and pathogenesis of dementia praecox as follows: Gastro-enteritis is the most constant and most characteristic somatic disorder in dementia praecox, irrespective of the clinical form and the duration of the psychosis. This fact, derived from clinical and anatomicopathologic studies, suggests the idea that there should be a relation of cause and effect between the gastro-intestinal pathologic changes and the psychosis. In normal conditions the liver and the internal secretion constitute a barrier protecting the organism from general and therefore also cerebral intoxication. When the focal infection is either very pronounced or of long duration, the protective organs may become involved, responding either by inflammation or by intoxication. Finally, a degenerative process may take place in these organs, more likely in those cases in which there is an inborn low resistance of the particular organs. The rupture of the "barrier" will remove the physiologic obstacle to the propagation of the primary gastro-intestinal intoxication.

Moreover, the secondary hepato-endocrine disturbances will produce an additional intoxication. The cerebrum will then be inundated by the "noxa" resulting from the two sources of intoxication. The author, in emphasizing the fact that he is fully cognizant of the important rôle of the hereditary predisposition in dementia praecox, also lays stress on the part played by "enterogenous" intoxication, which would ultimately be the essential factor in the process of the psychosis.

DIE STIGMATISIERTE THERESE NEUMANN VON KONNERSREUTH. By DR. FRITZ GERLICH. Volumes I and II. Price, 19 marks. Pp. 324 and 406. Munich: Josef Kosel and Friedrich Pustet, 1929.

The stigmatized Therese Neumann of Konnersreuth has given rise to a widespread discussion in which physicians have taken a justified part. Unfortunately they do not always reckon with the human factor in their work and utterances. At any rate, they lay themselves open to attempts on the part of laymen to show up the short circuits of both observation and reasoning. They seem to be short-sighted in ignoring the questions and arguments of nonmedical common-sense and nonmedical special pleading. Fritz Gerlich, a non-Catholic editor, with a degree of Ph.D. in history, lays down in two volumes, together of 730 pages, what he has to say after his analysis of his own observation and the literature. The result is an interesting exhibition of what will happen to a historian, to medicine and to "historical facts" when the layman goes in for "the truth" with the tools of his

special trade and without trained experience in the field under question. Physicians know what happens when lawyers arrogate the last word in psychiatry; they know also the cocksureness of the lay psychoanalyst, and here comes the historian with obviously quasilegal training. One has to read the sources and the two volumes to understand the striking satisfaction expressed in partisan "reviews of praise" of Gerlich's work, and the appearance of justification of distrust of the diagnosis of hysteria. Physicians will do well to dip into the two volumes to get a taste of their responsibilities and of the hazards to which one is exposed in dealing loosely with very human facts under inadequate conditions of study.

Gerlich, as chief editor of a Munich paper, was led to take an interest in the case because agitators demanded that the stigmatized person should be studied in a clinic. Scientific and political interests considered such a demand justified for the good of a sound public accounting. But public opinion balked at the idea that stigmatization and visions should become sufficient to deprive the miraculous person of her "liberty" and of the "right of disposal of her body" and defense against examinations as long as she was in no way "responsible" for the pilgrimages and the demonstrations of faith, etc.

Gerlich gives the layman's history of the case, with great situational detail. The eldest of eleven children of a poor tailor, Therese became a servant, doing practically a man's work on a farm of an innkeeper. She was averse to marriage and determined to become a mission sister. At the age of 20, in March, 1918, she helped in a fire, passing buckets of water, was urged to great effort and had a sudden pain in the back, numbness of the lower extremities, inability to bend, and vomiting after meals. She soon tried to work again, but in April had a renewed accident, a fall on the cellar steps with a bleeding wound in the occipital region, severe pain in the head on "coming to," incontinence and suffering in general. She was in a hospital from April 23 to June 10, 1918, with gastric complaints, hysterical fits and cessation of menses; in July, another fall was followed by visual disorders; there were renewed attempts to work and accidents, finally confinement in bed and blindness from March, 1919, till April, 1923, following an attack of vomiting "blood and pus"; she was able to read on the day of sanctification of the "little Therese of the child Jesus." By May 17, 1925, the paralysis, too, yielded suddenly with a religious experience and a sore on the back, which "had soaked the shirt with blood and pus," was suddenly cured. The vision of a light and hearing of the voice of her saint recurred on several occasions, and in November, 1925, cured her of appendicitis. On Good Friday, both eyes began to bleed; she was in frightful agony, with visions of the passion of Christ till the hour of the death of Christ; the next morning blood and pus came from an abscess of the right ear. She began to feel severe pain in the hands and feet, and both hands and both feet showed round open wounds with fresh blood flowing from them. Several weeks before Easter, an oblong wound had broken open in the cardiac region, occasionally with pure blood flowing from it. "Nobody who knows the young woman will speak of hysteria." For three years the young sufferer had not eaten any solid food and she was "weakened by the loss of blood." The following night the wounds dried up. The account abounds with detailed records of episodes of visions and stigmas of the thorns in her head, and equally full accounts of the precautions and corresponding dependability of the reporters and observers. In July, 1927, Therese was subjected to observation for fifteen days. Professor Ewald merely saw the reports, which appear rather contradictory.

Gerlich began his observations in September, 1927. He describes a usual normal state and occasions of an ecstatic state with visions of the history of Christ and of Saints, and states of participation in the bliss and omniscience of Christ. This is followed by a condition resembling the utterances and demeanor and naiveté of a child of 5, in which she sees the events (e. g., the kiss of Judas) as a friendly act without as yet any knowledge of what comes next. In this condition she also has been observed to speak Aramaic or Greek words and sentences, as during the visions of the murder of the children in Bethlehem.

The "critical review" of the medical and other discussions of the case in the press and in various publications making up the second volume is in its way remarkably illustrative of the way argument can create the "historical certainty" that Therese Neumann is neither hysterical nor an impostor. The technic of presentation might offer remarkable material for a study of the pitfalls of exegesis, but also the advantages of a method of argumentation which must give many a believing reader a sense of conviction and an impression of the undoubted superiority of the historian over the shortcomings of "psychoanalysis" and the contradictions of the quotations from medical literature. The book is to be recommended to physicians and lawyers for different reasons. It is a remarkable exhibition of the hazards of verbalization.

GESTALT PSYCHOLOGIE. By WOLFGANG KOHLER. Price, $4. Pp. 402. New York: Horace Liveright, 1929.

Progress in science has been made against the resistance of common sense. To those who can see only the obvious, each bit of scientific truth must come as a shock. Just as the philosopher and scientist have been about to agree that things are not what they seem, Kohler has presented himself with his Gestalt psychology. This is a glorification of the cult of common sense; "horse sense" might be a better term. His style is charming, and many of his ideas are stimulating, but one can almost see the thumb in the vest, and almost hear the patronizing: "Of course, that's so—common sense will tell you that!"

Kohler points out that a concept is more than a sum of its sensations; one might know all the notes that Beethoven used and yet, were that all one knew, one would know nothing of the ninth symphony. Psychology, as Kohler sees it, is an infantile science, pathetically striving to reach the level of hard realism which its brother sciences have attained; he chides it on its presumption in trying to be quantitative and objective; so young a science may be qualitative only. Even the physicist must use direct experience, and so realistic an instrument as an ammeter can be read only by the use of subjective sensations and understood only by subjective interpretations. Why then, he asks, should psychology scorn subjective data? Things surely existed before philosophers started to meditate about them, and the idea that the properties of an object reside in the observer does not correspond to actual reality. It is common sense that sensations give a real picture of the existing physical world, and that, Kohler feels sure, is all there is to it. The behaviorists he pooh poohs as being dogmatic and myopic; indeed, he convinces himself that the behaviorists are guilty of introspection!

Organisms react not to single stimuli, but to constellations of stimuli; an isolated stimulus is an artefact. Furthermore, the organism responds, it does not merely transmit. From each part of an organized object stimuli reach a sensory end-organ; they are separate stimuli, constituting a mosaic that the organism blends into a picture which by some strange chance always corresponds to the object that initiated it. To be sure the sensation, even the conception, may vary with the attitude of the observer as well as with fortuitous circumstances; the physical reality of the object, however, persists. Common sense tells him that.

A Gestalt is a segregated whole; it is a form which is intrinsic in an object's reality; one may change the tempo and key of a tune to a certain extent, and still recognize the melody; it has preserved its Gestalt. If one changes it more, one can no longer recognize it as the same tune; its Gestalt has been destroyed. One first senses wholes—Gestalten; one analyzes them later. A sentence is not appreciated as if it were made up of separate words, much less of letters; its meaning is carried in its whole form, its Gestalt. When one divides into words, and breaks the words into letters, one is doing something unnatural. Direct experience always gives one first the Gestalt.

Kohler credits himself with a rediscovery of the obvious. He would be the first to acknowledge that it is indeed true that psychology is the discovery by the professors of what every one else has always known.

BODILY CHANGES IN PAIN, HUNGER, FEAR AND RAGE. By WALTER B. CANNON, M.D., S.D., LL.D. Second edition. Price, $3. Pp. 404. New York: D. Appleton & Company, 1929.

The first edition of this book was published in 1915. It was given to the scientific world by Dr. Walter B. Cannon, who is at present the George Higginson Professor of Physiology in Harvard University, as an account of recent researches into the function of emotional excitement. It took immediate first rank as a contemporary classic in the scientific literature and now reposes firmly on that shelf of famed volumes that contain the works of the immortal William Harvey, Claude Bernard and their illustrious successors.

From the original nucleus of Dr. Cannon's laboratory a chain of colonies of men continuing and adding to his labor has grown out and circled the globe. They are to be found in Japan, Russia, England, Algiers, Argentina and elsewhere. For this to occur in a man's lifetime is highly distinctive, and Dr. Cannon is still young!

This second edition of "Bodily Changes in Pain, Hunger, Fear and Rage" includes a large accumulation of new evidence that has been gathered by Dr. Cannon and his associates since the appearance of the first edition a little over fifteen years ago. The general thesis of the entire work is that bodily changes which attend great excitement are directed toward efficiency in physical struggle.

Attention to the second edition needs to be called only to bring notice of its additional contents. Five chapters have been added that are of particular interest to neurologists and psychiatrists. They report data collected on special topics. One is on the emotional derangement of bodily functions. One chapter is on thirst, and two chapters consider the theories of emotion. These two chapters present a critical review of the James-Lange theory and an alternative theory suggested by the researches of Dr. Cannon and by the researches of his associates, to whom, by the way, his opus is dedicated.

HANDWÖRTERBUCH DER MEDIZINISCHEN PSYCHOLOGIE. Edited by DR. KARL BIRNBAUM. Price, 48 marks. Pp. 668. Leipzig: Georg Thieme, 1930.

This medical psychology in the form of a dictionary offers in compact solid articles a presentation of the topics of psychology and psychiatry. The general topics of psychopathology and the psychoses are largely covered by Birnbaum and by Kronfeld, Kahn and Lange, the psychoanalytic topics by Hartmann, the sex topics by Marcuse and Gruhle, heredity by Kahn, constitution by Jaensch, normal psychology by S. Fischer, motility by Bostroem, etc.

The work in this way represents the conceptions of the younger leading workers of Germany, while the foreign literature receives little attention. As a picture of a broad cross-section of German medical thought in psychology and psychopathology, the book offers unusual material. For another edition it might be well to make some topics of the life work and life tendencies of some of the outstanding workers in the field, similar to what Birnbaum gave in Bumke's Handbuch. It could be done in concise form and would give precision to lines of divergent and convergent thought, methods and results, and also would avoid omissions.

That anxiety is treated only under "Schreckneurose" limits the discussion of the topic. In other ways more concreteness and directness might be attained by a topical discussion of reactions and reaction sets, in the manner of the American mode of approach. But each group of workers and teachers has the right to its own selection of topics, and Birnbaum has succeeded in bringing out a remarkable sampling of valuable material, infinitely better than any of our own collective attempts of "readers" in psychopathology.

AERZTE ALS PATIENTEN. By DR. A. GROTJAHN. Price, 14 marks. Pp. 268. Leipzig: Georg Thieme, 1929.

One speaks occasionally of our age as that of the interest in the child — one might add "and of the individual." In this very worth while book, Grotjahn gives samples of crucial experiences of physicians in their own illnesses, a much appreciated gathering of data for a better knowledge of the personality reaction of patients. Psychiatry and nervous diseases figure in several reports. The material is grouped under the heading of subjective accounts of illnesses obtained out of physicians' autobiographies, accounts from casuistic literature and responses to several inquiries and requests by the editor. The book is a real stimulus in the direction of practical medical psychology — examples of physicians describing their having to take their own medicine and, more, having to prove themselves as patients.

THE COMMON SENSE OF DRINKING. By RICHARD R. PEABODY. Price, $2. Pp. 190. Boston: Little, Brown & Company, 1931.

The author is a psychologist, not a physician; from the contents of the book it is obvious that he has specialized with and is treating inebriates, and from his own account successfully. He does not discuss the physical aspects of alcoholism, but is concerned solely with the psychology of the patients. There is nothing new in this presentation. Psychologists should not treat patients with mental disorders; that is not their function. It should be done by physicians.

DIE PSYCHANALYSE IM DIENSTE DER ERZIEHUNG. By DR. O. PFISTER. Third edition. Price, 4 marks. Pp. 160. Leipzig: Julius Klinkhardt, 1929.

The third edition of this little book, like all the publications of the writer, combines an appreciation of the moral-religious aspects of life with a clear presentation of the psychoanalytic principles of the freudian school. An English translation of the first edition is available. The German style is direct and readable.

LA PRACTIQUE DE L'IONISATION. APPLICATIONS MEDICO-CHIRURGICALES. By PIERRE ROUSSEAU and PIERRE NYER. Price, 32 francs. Pp. 167. Paris: Gaston Doin, 1931.

The practice of ionization is not well known, at least among American neurologists, and the subject is discussed from the French point of view. The book is divided into three parts: the first discusses the historical aspect, giving the technical points of view; the second presents the effects on the tissues, and in the third, the practical applications are given.